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Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

03405719.0

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For the President of the European Patent Office

Le Président de l'Office européen des brevets
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R C van Dijk

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Novel hypocholesterolemic compounds

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Lipideon

Novel hypocholesterolemic compounds

The present invention relates to novel hypocholesterolemic compounds useful in the treatment and prevention of atherosclerosis and for the reduction of cholesterol levels as well as to pharmaceutical compositions comprising said compounds alone or in combination with other active agents.

Atherosclerotic coronary heart disease represents the major cause for death and cardiovascular morbidity in the western world. Risk factors for atherosclerotic coronary heart disease include hypertension, diabetes mellitus, family history, male gender, cigarette smoke as well as serum cholesterol. Elevated concentrations of serum cholesterol have been demonstrated by a number of clinical studies to be a major contributing factor in the development and progression of atherosclerosis, which is characterized by the formation of cholesterol-containing plaques in the aorta and lesser arteries.

In mammals, 1/3 of the serum cholesterol is derived from exogenous dietary sources which enters the body through absorption in the intestine and 2/3 of the serum cholesterol are derived through endogenous de novo synthesis in the liver involving a complex set of enzyme-catalyzed reactions and regulatory mechanisms.

Recently it has been shown that intestinal cholesterol absorption is an energy-independent, protein-mediated process (Hauser, H. et al, *Biochemistry* **1998**, *37*, 17843-17850; Schulthess, G. et al, *Biochemistry* **2000**, *39*, 12623-12631; Werder, M. et al, *Biochemistry* **2001**, *40*, 11643-11650) rather than a passive diffusion process. The proteins facilitating intestinal cholesterol absorption were identified as two brush border membrane-resident scavenger receptors (Hauser, H. et al, *Biochemistry* **1998**, *37*,

17843-17850; Werder, M. et al, *Biochemistry* **2001**, *40*, 11643-11650). Both *in vitro* and *in vivo* animal experiments confirmed the presence of these two scavenger receptors in the intestinal BBM and proved that they are responsible for the protein-mediated cholesterol uptake.

Various 2-azetidinone compounds have been reported as being useful in lowering cholesterol and/or in inhibiting the formation of cholesterol-containing lesions in mammalian arterial walls: For example WO 93/02048, WO 94/17038, WO 95/08532, PCT/US95/03196, U.S. Pat. No.5,633,246 describe 2-azetidinone compounds with different substituents at the 3-position, and U.S. Pat. No. 5,756,470 discloses 2-azetidinones having varying substituents at the 4 position. Other azetidinone derivatives include for example elastase inhibitory substituted azetidinones disclosed in European Patent 199,630B1 and European Patent Application 337,549A1. The most prominent representative of these 2-azetidinones, Ezetimibe (also known under trade names Zetia™ and Ezetrol®), has been in use as a cholesterol-lowering drug in monotherapy and in dual therapy combined with a statin. It is the first representative of the new class of cholesterol-lowering drugs that inhibit intestinal cholesterol absorption by targeting the two scavenger receptors in the intestinal brush border membrane described above.

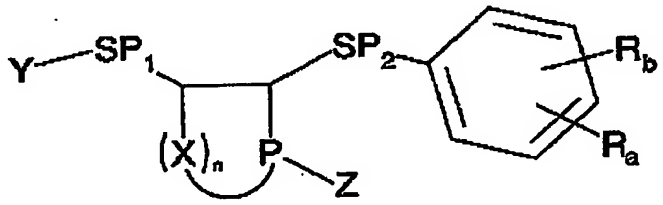
However, it has been shown that the 2-azetidinones upon administration are readily absorbed and extensively metabolized into the pharmalogically active glucuronide of which over 95% remained in the intestinal wall upon direct administration as the glucuronide (van Heek, M. et al. *Br. J. Pharmacol.* **2000**, *129*, 1748-1754). In addition side effects such as allergic reactions including rash and angiodema have been reported.

Applicants have now discovered that the compounds of the present invention with the structural characteristics as depicted in

formula I and in particular formulas II and III are able to inhibit the protein-mediated process mentioned above by which cholesterol absorption is mediated, while overcoming the above described disadvantages of compounds known in the art. Thus the compounds of the present invention are particularly useful in the treatment and prevention of atherosclerosis and for the reduction of cholesterol levels.

In a first aspect, the present invention thus relates to novel hypocholesterolemic compounds of formula I, and in particular to compounds of formulas II and III having a four- or five-membered ring, respectively.

In one embodiment, the present invention is directed to a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof,



I

wherein

P represents -N< or -C=,

X represents independently of each other $-CH_2-$, CR_1 (sp_2-hybridised), O, -NH-, =N-, -CO- or -CS-, wherein R_1 represents H or NR_2, wherein R_2 represents H or lower alkyl, which optionally is linked to Z such that a bicyclic structure is formed;

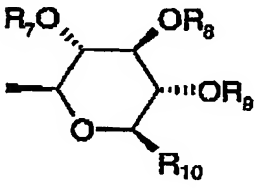
n represents 1 or 2,

R_a represents H, lower alkyl, $-OR_3$, $-O(CO)R_3$, $-O(CO)OR_3$, $-O(CO)NR_3R_4$, $-NR_3R_4$, $-NR_3(CO)R_4$, $-COOR_3$, $-CONR_3R_4$, -

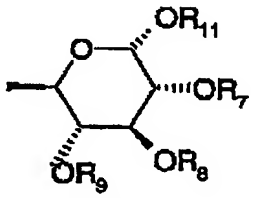
$CH=CHCOOR_3$, $-CF_3$, $-CN$, $-NO_2$, SO_3H, PO_3H or halogen, wherein R_3 and R_4 represent H or lower alkyl,

R_b represents H, OH, $-OSO_2Me$, $-OSO_2W$ wherein W represents optionally substituted aryl or heteroaryl, $-OCO(CHOH)_2COOR_5$ wherein R_5 represents H or lower alkyl; or represents the formula $-Sp_3-R_6$,

wherein Sp_3 represents a covalent bond, $-O-$, $-OCH_2-$, $-OSO_2CH_2-$, $-OSO_2-$, $-OSO_2-(p)C_6H_4O-$ and R_6 represents one of carbohydrate structures A-D:



A



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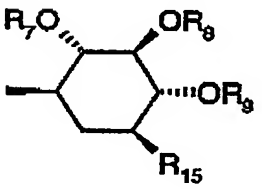
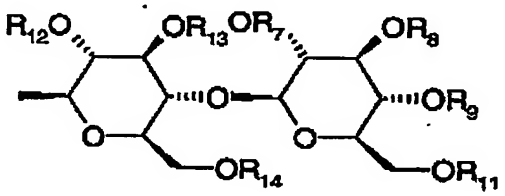


C



D

wherein

R_7, R_8, R_9, R_{11}, R_{12}, R_{13} and R_{14} represent independently of each other H, lower alkyl, aryl(lower alkyl), -CO-lower alkyl, -CO-aryl, $-SO_3^-$ or $-PO_3^-$,

R_{10} represents $-CH_2OR_{16}$ or $-COOR_{17}$, and

R_{15} represents $-CH_2OR_{16}$, $-COOR_{17}$, $-CH_2NH_2$, $-CH_2OPO_3^-$ or $-CH_2OSO_3^-$, wherein R_{16} and R_{17} independently of each other represent H, lower alkyl, aryl(lower alkyl), -CO-lower alkyl, -CO-aryl, $-SO_3^-$ or $-PO_3^-$,

Z represents optionally substituted aryl or heteroaryl,

Sp_1 represents a spacer unit, such as a straight-chain or branched lower alkyl group $-(CH_2)_p-$, wherein p is from 2-6, which is unsubstituted, mono or poly-substituted by -OH, $-OR_{18}$, halogen or cyano group, wherein one or more $-CH_2-$ groups may independently be replaced by -O-, -CO-, -CO-O-, -O-CO-, $-NR_{19}-$, $-NR_{19}-CO-$, $-CO-NR_{19}-$, -CH=CH-, -C≡C- -and wherein R_{18} and R_{19} represent a hydrogen atom or lower alkyl;

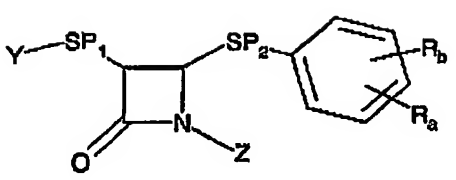
Sp_2 represents an optional spacer unit, such as a covalent bond or a straight-chain or branched lower alkyl group $-(CH_2)_q-$, wherein q is from 1-6, which is unsubstituted, mono or poly-substituted by -OH, $-OR_{20}$, halogen or cyano group, wherein one or more $-CH_2-$ groups may independently be replaced by -O-, -CO-, -CO-O-, -O-CO-, $-NR_{21}-$, $-NR_{21}-CO-$, $-CO-NR_{21}-$, -CH=CH-, -C≡C- -and wherein R_{20} and R_{21} represents a hydrogen atom or lower alkyl;

Y represents optionally substituted aryl or heteroaryl,

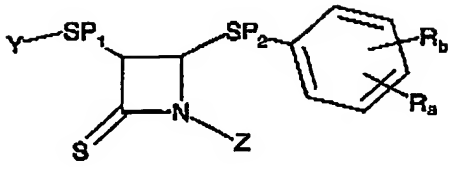
with the proviso, that if P = -N<, n=1, X = -CO- and Sp_2 represents a covalent bond, R' may not represent carbohydrate structures A or D for Sp_3 = -O- and R_6 may not represent carbohydrate B for $Sp_3 = -OCH_2-$.

In a preferred embodiment, the present invention is directed towards compounds of formula I wherein P = -N<, n = 1 and X = -CO-, -CS-, $-CH_2-$ or -NH-.

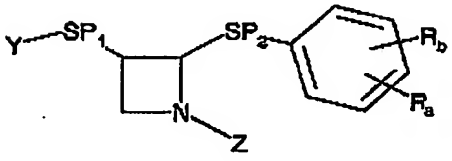
Thus, the present invention is preferably directed towards compounds of formula IIa-d



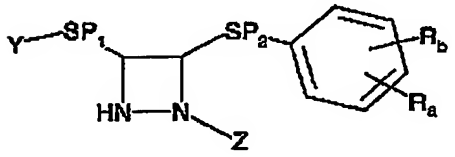
IIa



IIb



IIc



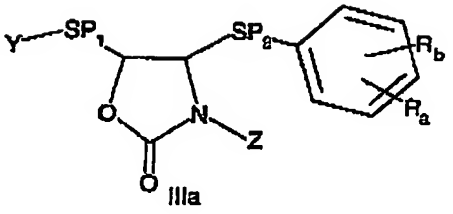
IId

or a pharmaceutically acceptable salt or solvate thereof,

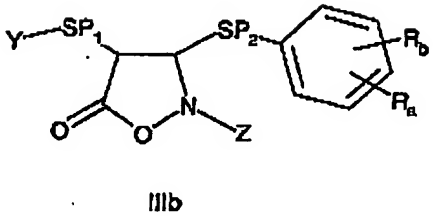
wherein the groups R_a, R_b, Sp_1, Sp_2, Y and Z are as defined above.

In another preferred embodiment, the present invention is directed towards compounds of formula I wherein for P = -N<, $-(X)_n-$ represents -OOC-, -COO-, -CONH-, -CH=N-, and for P = -C=, $-(X)_n-$ represents -NH-N= or -O-N=.

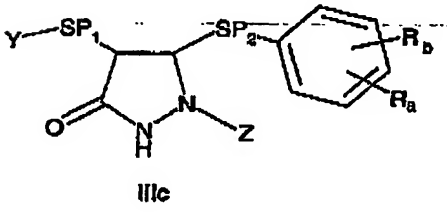
Thus, the present invention is directed towards compounds of formula IIIa-f:



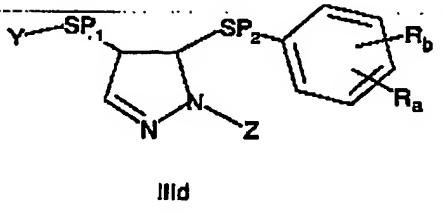
IIIa



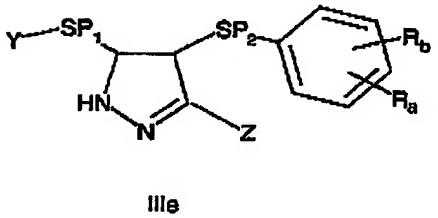
IIIb



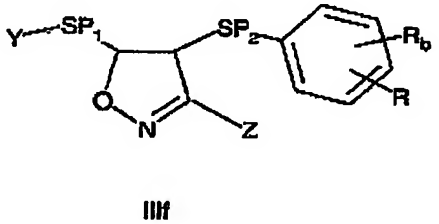
IIIc



IIId



IIIe



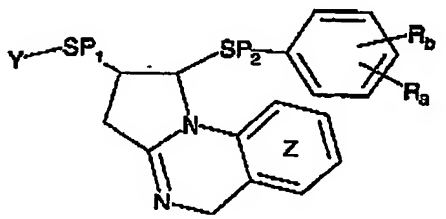
IIIf

or a pharmaceutically acceptable salt or solvate thereof,

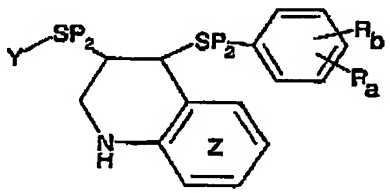
wherein the groups R_a, R_b, Sp_1, Sp_2, Y and Z are as defined above.

In a further preferred embodiment, the present invention is directed towards compounds of formula I with P = -N< where $-(X)_n-$ represents -CH-C=NR- and -CH-NH-CR- and wherein ring Z is coupled to $-(X)_n-$ to form bicylic compounds.

Thus, the present invention is further directed towards compounds of formula IIIg-h:



IIIg



IIIh

R_a preferably represents H, lower alkyl, $-OR_3$, $-NR_3R_4$, $-COOR_3$, $-CONR_3R_4$, $-CH=CHCOOR_3$, $-CF_3$, $-CN$, $-NO_2$, SO_3H, PO_3H or halogen, more preferably H, lower alkyl, $-OR_3$, $-NR_3R_4$, $-COOR_3$, $-CONR_3R_4$ or halogen, most preferably H, lower alkyl, $-OR_{19}$ or halogen, wherein R_3 and R_4 represent independently of each other H or lower alkyl.

R_b preferably represents H, OH, $-OSO_2Me$, $-OSO_2W$ wherein W represents Phenyl (Ph) or isomers of salicylic acid (all combinations of disubstituted phenyl with OH and COOH substituents); or the formula $-Sp_3-R_6$, wherein Sp_3 preferably represents a covalent bond, $-O-$, $-OCH_2-$ or $-OSO_2CH_2-$ and R_6 represents one of carbohydrate structures A-D, preferably carbohydrate structures A, B or D. More preferably R_b represents H, OH, $-OSO_2Me$, $-OSO_2Ph$; or the formula $-Sp_3-R_6$, wherein Sp_3 preferably represents a covalent bond, $-O-$, $-OCH_2-$ or $-OSO_2CH_2-$ and R_6 represents one of carbohydrate structures A-D, preferably carbohydrate structures A, B or D.

Sp_1 preferably represents a straight-chain or branched $-(CH_2)_m-$ group, which is unsubstituted, mono or poly-substituted by $-OH$, $-OR_{18}$, halogen or cyano group, wherein R_{18} represents hydrogen or lower alkyl and m is 1 to 3. More preferably Sp_1 represents a $-(CH_2)_3-$, which is unsubstituted or substituted by $-OH$ or halogen.

Sp_2 preferably represents a straight-chain or branched $-(CH_2)_p-$ group, which is unsubstituted, mono or poly-substituted by $-OH$, $-OR_{20}$, halogen or cyano group, wherein R_{20} represents hydrogen or lower alkyl and p is 1 to 3. More preferably Sp_1 represents an unsubstituted $-(CH_2)_p-$, wherein p is 1 to 3, most preferably a covalent bond.

R_{15} preferably represents $-CH_2OR_{16}$, $-COOR_{17}$ or $-CH_2NH_2$, wherein R_{16} and R_{17} independently of each other represent H, lower alkyl, aryl(lower alkyl), -CO-lower alkyl, -CO-aryl, $-SO_3^-$ or $-PO_3^-$, preferably H, acetyl or benzyl.

R_7, R_8, R_9, R_{11}, R_{12}, R_{13}, and R_{14} preferably represent independently of each other H, lower alkyl, aryl-lower alkyl, -CO-lower alkyl, -CO-aryl, more preferably, H, acetyl or benzyl.

The term "optionally substituted aryl group" should be understood to include an aromatic ring system having 4 to 10, preferably 5, 6 or 10 ring atoms. The aryl group can be substituted with one or more substituents, which may be the same or different, and are selected from a group as defined hereinafter. Non-limiting examples of suitable aryl groups include phenyl, naphthalene or tetraline groups, most preferably phenyl groups substituted by halogeno, preferably fluoro.

The term "optionally substituted heteroaryl" should be understood to include an aromatic ring system of 5 to 14, preferably 5 to 10, more preferably 5 to 6 or 10 ring atoms, in which one or more of the atoms in the ring system is/are atoms other than carbon, for example nitrogen, oxygen or sulfur. The heteroaryl can be optionally substituted by one or more substituents, which may be the same or different, and are selected from a group as defined hereinafter. Examples of suitable 6-membered heteroaryl groups include pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl and the like. Examples of useful 5-membered heteroaryl rings include furyl, thienyl, pyrrolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxazolyl and isoxazolyl. Useful bicyclic groups are benzo-fused ring systems derived from the heteroaryl groups named above, e.g., quinolyl, phthalazinyl, quinazolinyl, benzofuranyl, benzothienyl and indolyl.

The term "lower alkyl" should be understood to include straight chain and branched hydrocarbon groups having from 1 to 8, preferably 1 to 6, more preferably from 1 to 3 carbon atoms, which may be optionally substituted. Non-limiting examples of suitable lower alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, fluoromethyl and trifluoromethyl.

The term "branched" should be understood to represent a linear straight chain hydrocarbon group having one or more lower alkyl groups such as methyl, ethyl or propyl, attached to it.

The term "lower alkoxy" should be understood to include "lower alkyl-O-"-groups, wherein the lower alkyl groups are as described above and have from 1 to 8, preferably 1 to 6, more preferably from 1 to 3 carbon atoms. Methoxy, ethoxy and isopropoxy groups are especially preferred.

The term "aryl(lower alkyl)" should be understood to include an aryl(lower alkyl)group in which the aryl and lower alkyl are as previously described. Non-limiting examples of suitable aryl(lower alkyl) groups include benzyl, phenethyl and naphthlenylmethyl.

If not otherwise indicated, the term "optionally substituted" should be understood to represent substituents independently selected from the group consisting of aryl, heteroaryl, aryl(lower alkyl), (lower alkyl)aryl, aralkenyl, heteroaralkyl, alkylheteroaryl, heteroaralkenyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halogen, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, aminoalkyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, cycloalkenyl, heterocyclyl, heterocyclenyl, preferably lower alkyl, hydroxy, lower alkoxy, cyano, alkylthio, amino, -NH(lower alkyl), -N(lower alkyl)2 (which alkyls can be the same or different), carboxy, -C(O)O-(lower alkyl) and halogen. Those skilled in the art will recognize that the size and nature of the substituent(s) will affect the number of substituents which can be present.

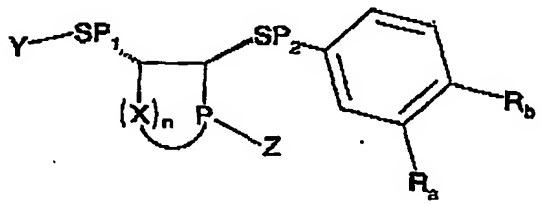
The term "halogen" should be understood to include fluoro, chloro, bromo. iodo, preferably, fluoro and chloro, most preferably, fluoro.

It is understood that all isomers, including enantiomers,

stereoisomers, rotamers, tautomers and racemates of the compounds of formula I and in particular the compounds of formulas II and III are contemplated as being part of this invention. The invention includes stereoisomers in optically pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting optically pure or optically enriched starting materials or by separating isomers of a compound of formula I and in particular the compounds of formulas II and III. In a preferred embodiment the stereochemistry in the central ring is such that the substituents at the 3- and 4-position are in trans configuration to each other.

In yet a further embodiment, preferred combinations of groups R_a and R_b include combinations wherein R_b is as defined hereinabove and is in para-position (in relation to the linker Sp_2) and R_a is as defined hereinabove, most preferably H, and is in meta-position.

Thus in a further preferred embodiment the present invention is directed towards a compound of formula IVa,

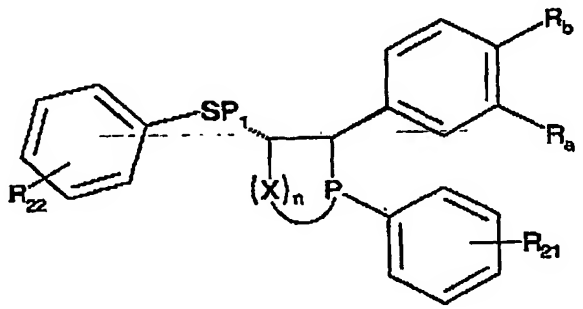


IVa

wherein R_a, R_b, Sp_1, Sp_2, P, X, Y, Z and n are as defined hereinabove.

Further preferred embodiments include combinations, wherein Sp_2 is a covalent bond and Y and Z represent optionally substituted phenyl rings.

Thus in a further preferred embodiment the present invention is directed towards a compound of formula IVb,



IVb

wherein R_a, R_b, Sp_1, P and X are as defined hereinabove and wherein R_{21} and R_{22} preferably represent H, lower alkyl, lower alkoxy or halogen, most preferably in para-position.

Compounds of formula I and in particular compounds of formulas II and III may be prepared using methods of preparation kwnon in the art and are described in the following paragraphs:

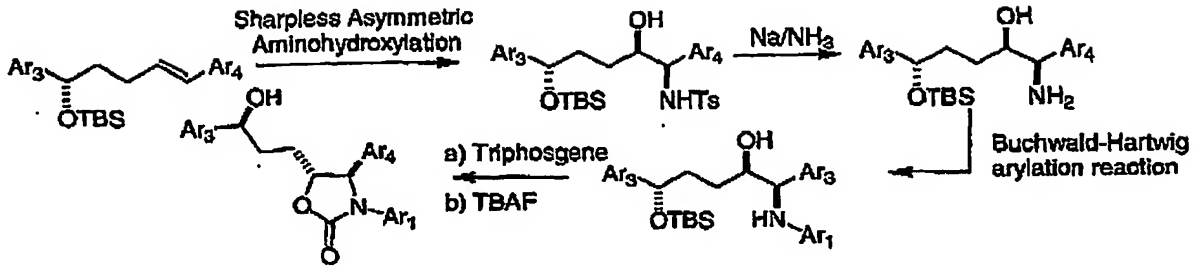
The 2-azetidinone portions of the compounds of formula II can be prepared by known methods, such as are disclosed in U.S. Pat. Nos. 5,631,365, 5,756,470, 5,767,115, 5,846,966, 6,207,822, U.S. Provisional Patent Application No. 60/279,288 filed Mar. 28, 2001, and PCT Patent Application WO 93/02048, each of which is incorporated herein by reference. Compounds of formula IIa according to the invention may then be obtained by further linkage to appropriate carbohydrate structures using literature procedures as illustrated by the Examples.

Compounds of formula IIb may be obtained through conversion of β-lactams to thiolactams, most commonly performed with Lawesson's reagent (Verkoyen, C. and Rademacher, P. *Chem. Ber.* **1985**, *118*, 653-660; Yde, B. et al. *Tetrahedron* **1984**, *40*, 2047-2052; Steliou, K.; Mrani, M. *J. Am. Chem. Soc.* **1982**, *104*, 3104-3106;

Clader, J. W. et al. *J. Med. Chem.* **1996**, *39*, 3684-3693).

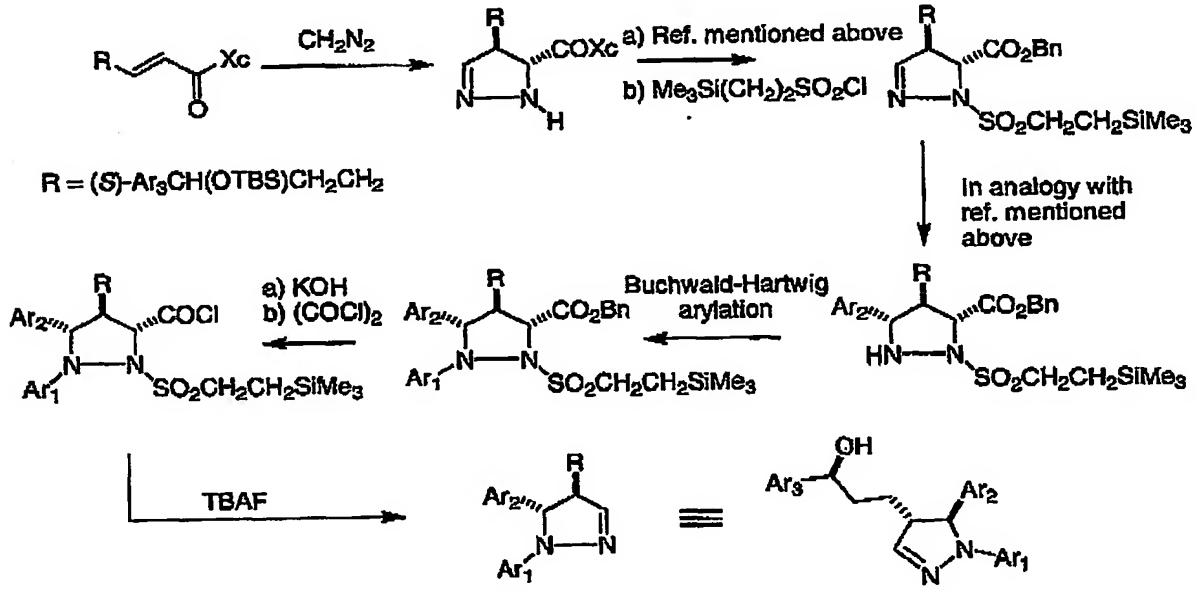
Compounds of formula IIc may be obtained through conversion of β-lactams to azetidines, which may be achieved by a number of wellknown methods in the art, such as (1) direct one-step reduction with reducing agents of the composition AlH_xCl_{3-x}, such as chlorodihydroalane or alane (Jackson, M. B. et al. *Aust. J. Chem.* **1983**, *36*, 779), or diborane (Jackson, M. B. et al.; *Aust. J. Chem.* **1983**, *36*, 779-788), $AlHCl_2$ and DIBAL-H (Yamashita, M. and Ojima, I. *J. Am. Chem. Soc.* **1983**, *105*, 6339-6342; Ojima, I. et al. *J. Org. Chem.* **1991**, *56*, 5263-5277); and (2) cyclodehydration of 1,3-amino alcohols using various methods (Sohar, P. et al. *Chem. Soc. Perkin Trans. 2* **2000**, 287-293; Suga, H. et al. S. *J. Am. Chem. Soc.* **1994**, *116*, 11197-11198; Barluenga, J. et al. *Tetrahedron* **1996**, *52*, 3095-3106; Obika, S. et al. *Tetrahedron Lett.* **2003**, *44*, 5267-5270).

The preparation of compounds of formula IIIa is effected as outlined in Scheme I through initial Sharpless asymmetric amino hydroxylation reaction of the desired trans-1,2-disubstituted alkenes (Demko, Z. P. et al. *Org. Lett.* **2000**, *2*, 2221-2223; O'Brien, P. *Angew. Chem. Int. Edit. Engl.* **1999**, *38*, 326-329; Bodkin, J. A.; McLeod, M. D. *J. Chem. Soc. Perkin Trans. 1* **2002**, 2733-2746), followed by chromatographic separation to obtain the desired regioisomeric product. Subsequent cleavage of the *para*-toluene sulfonamide group furnishes a primary amine which upon Buchwald-Hartwig arylation reaction (Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852-860; Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805-818) and subsequent exposure to triphosgene eventually leads to the formation of the desired oxazolidinones of formula IIIa.



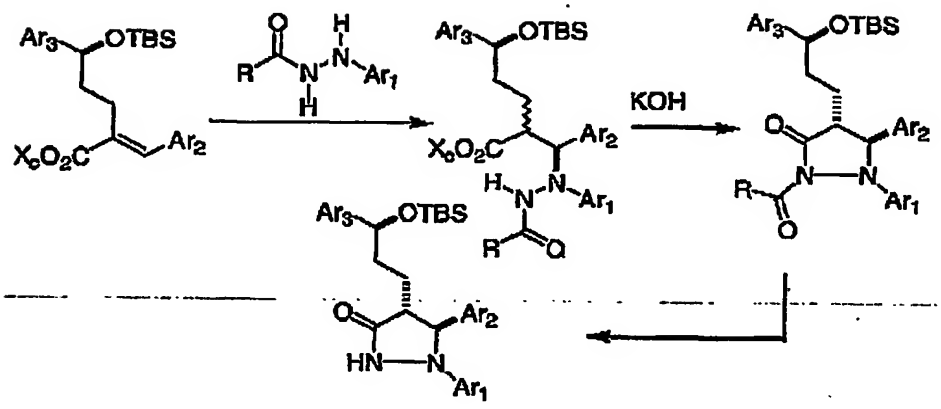
Scheme 1

Compounds of formula IIIe may be obtained e.g. as illustrated in Scheme II using known methods in the art (Mish, M. R. et al. *J. Am. Chem. Soc.* **1997**, *119*, 8379-8380; Guerra, F. M. et al. *Org. Lett.* **2000**, *2*, 4265-4267).



Scheme II

The preparation of pyrazolidinones of formula IIIc proceeds in an analogous strategy to that reported in the literature as illustrated in Scheme III (Lou, B. S. et al. *J. Org. Chem.* **1995**, *60*, 5509-5514; Tomkinson, N. C. O. *Rodd's Chemistry of Carbon Compounds (2nd Edition), Asymmetric Catalysis, Ed. M. Sainsbury* **2001**, *5*, 199-258).



Scheme III

It has been shown that the compounds of the invention display superior pharmacological activities and are able to overcome the drawbacks of known cholesterol-lowering agents using well-established methods in the art, e.g. evaluation of their IC_{50} value for cholesterol uptake in rabbit brush border membrane vesicles (BBMV) as well as in Caco-2 cells (Hauser, H. et al, *Biochemistry* **1998**, *37*, 17843-17850; Schulthess, G. et al, *Biochemistry* **2000**, *39*, 12623-12631; Werder, M. et al, *Biochemistry* **2001**, *40*, 11643-11650; Boffelli, D. et al. *FEBS Lett.* **1997**, *411*, 7-11) (see also Table I).

Thus, the compounds of the invention, e.g. compounds of formula I and their pharmaceutically acceptable acid addition salts, exhibit pharmacological activity and are, therefore, useful as pharmaceuticals. The compounds of the invention have been shown to effectively inhibit cholesterol absorption and are therefore useful in the treatment and/or prevention of atherosclerosis and of the reduction of cholesterol levels.

Thus in yet a further aspect, the present invention is directed to a method of treatment and/or prevention of atherosclerosis, of the reduction of cholesterol levels and of treating or preventing a vascular condition, comprising administering to a mammal in need of such treatment an effective amount of a compound of formula I and in particular a compound of formulas II and

III.

The novel compounds of formula I can be used, for example, in the form of pharmaceutical compositions containing a therapeutically effective amount of the active ingredient, if appropriate together with inorganic or organic, solid or liquid, pharmaceutically acceptable carriers suitable for enteral, e.g. oral, or parenteral administration. Accordingly, tablets or gelatin capsules are used that contain the active ingredient together with diluents, typically lactose, dextrose, saccharose, mannitol, sorbitol, cellulose and/or lubricants, e.g. diatomaceous earth, talcum, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Tablets may also contain binders, typically magnesium aluminium silicate, starches, typically corn starch, wheat starch, rice starch or arrow root starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and, if desired, disintegrators, typically starches, agar, alginic acid or a salt thereof, e.g. sodium alginate, and/or effervescent mixtures, or absorbents, colourants, flavourings and sweeteners.

Thus in another aspect, the invention relates to a pharmaceutical composition comprising a compound of formula I, and in particular a compound of formulas II and III (and optionally other therapeutically effective agents), and a pharmaceutically acceptable carrier for the treatment or prevention of artheriosclerosis or for the reduction of cholesterol levels.

The terms "effective amount" and "therapeutically effective amount" mean that amount of a compound of formula I and in particular compounds of formulas II and III (and optionally other therapeutically effective agents), that will elicit a biological or medical response of a tissue, system, animal or mammal, which includes alleviation of the symptoms of the condition or disease being treated and the prevention, slowing or halting of progres-

sion of one or more conditions, for example atherosclerosis, hypercholesterolemia.

The pharmaceutical compositions so obtained which, if desired, contain further pharmacologically active substances, are prepared in a manner known per se by conventional mixing, granulating, sugar-coating, solution or lyophilising methods and contain from about 0.1% to 100%, preferably from about 1% to about 50%, lyophilisate to about 100%, of active ingredient.

The compounds, compositions and treatments of the present invention can be administered by any suitable means which produce contact of these compounds with the site of action in the body, for example in the plasma, liver or small intestine of a mammal or human. Thus the novel compounds of formula I may also be used in the form of compositions for parenteral, oral, transdermal administration or infusion solutions. Such solutions are preferably isotonic aqueous solutions or suspension which, e.g. in the case of lyophilised compositions that contain the active ingredient by itself or together with a carrier, such as mannitol, can be prepared before use. The pharmaceutical compositions can be sterilised and/or can contain excipients, typically preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers.

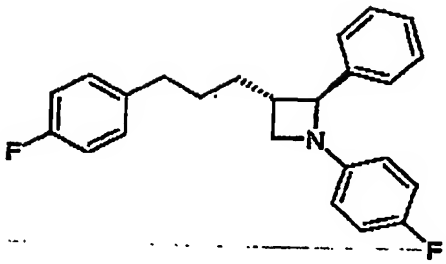
In yet a further aspect, the invention relates to a kit comprising an effective amount of a compound of formula I and in particular a compound of formulas II and III in a pharmaceutically acceptable carrier (and optionally an effective amount of another therapeutically effective agent), optionally in separate compartments.

The following non-limiting Examples illustrate the above-described invention in more detail.

EXAMPLES

Materials and Methods: Reactions in anhydrous solvents were all performed using oven dried glassware under an atmosphere of argon. Reagent grade solvents were all purchased from chemical companies and used without prior purification. For chromatic purification, technical grade solvents were distillated prior to use. TLC was performed using Machery-Nagel Alugram Sil G/UV_{254} TLC plates and visualized with ultraviolet light at 254 nm and 12 g phosphor molybdic acid in 250 mL EtOH or 10% H_2SO_4 in MeOH (v/v). Chromatographic purification of products was accomplished using dry column vacuum chromatography on Merck Silica Gel 60 (15 - 40 µm) according to literature procedures (Pedersen, D. S. and Rosenbohm, C. *Synthesis* **2001**, 2431-2434); fractions containing product were pooled, the solvents were evaporated under reduced pressure and the residue was dried under high vacuum to give the product. NMR spectra were recorded on a Varian Mercury 300MHz apparatus operating at 300 MHz and 75 MHz for ^1H and ^{13}C, respectively, and chemical shifts (δ) were referenced to the internal solvent signals. IR-Spectra were recorded in $CHCl_3$ on a Perkin Elmer Spectrum RX I FT-IR apparatus (thin films on NaCl plates) and are reported as absorption maxima in cm^{-1}. Elemental analysis was performed by the Mikroelementaranalytisches Laboratorium at the ETH, Zürich. High resolution matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS) was recorded in positive ion mode.

Example 1



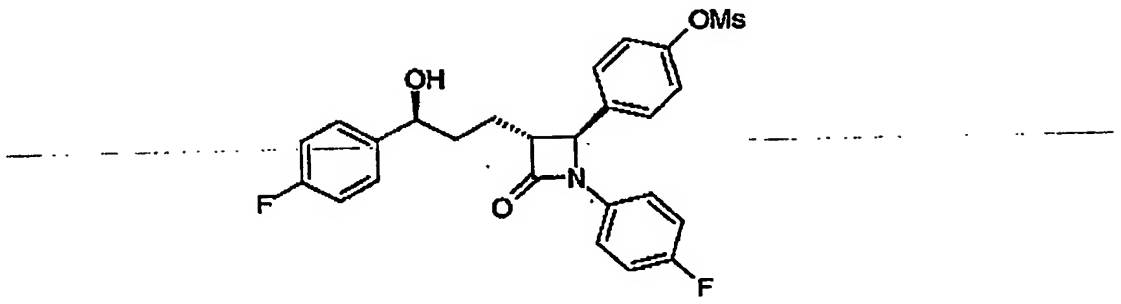
V

$LiAlH_4$ (114 mg, 3.0 mmol) and $AlCl_3$ (390 mg, 2.9 mmol) were suspended in anhydrous ether (15 mL) and refluxed for 30 min. Trans-1-(4-fluorophenyl)-3-[(3-phenyl)-propyl]-4-phenyl-2-azetidinone (361 mg, 1.00 mmol; prepared according to Browne, M. et al. Tetrahedron Lett. **1995**, *36*, 2555-2558) dissolved in anhydrous ether (15 mL) was added and after stirring at reflux for 30 min, the suspension was cooled and H_2O (5 mL) was added dropwise followed by addition of 50% sat. aq. $NaHCO_3$ (30 mL). The layers were separated, the aqueous layer was extracted with EtOAc/hexane and ether and the combined organic layer was washed successively with sat. aq. $NaHCO_3$ (20 mL) and H_2O (20 mL), evaporated on celite and purified by dry column vacuum chromatography (3.7 x 3.3 cm) on silica gel eluting with a gradient of 0-10% EtOAc in hexane (v/v) to give the desired compound **V** (281 mg, 81%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.51-7.14 (10H, m), 6.87 (2H, t, J = 8.7 Hz), 6.38 (2H, dd, J = 4.7, 9.0 Hz), 4.46 (1H, d, J = 6.8 Hz), 4.17 (1H, t, J = 6.8 Hz), 3.35 (1H, dd, J = 6.8, 7.5 Hz), 2.69-2.58 (3H, m), 1.85-1.56 (4H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 157.64, 154.52, 148.53, 142.69, 141.95 (C), 128.66, 128.25, 127.47, 125.99, 125.73, 115.41, 115.12, 113.04, 112.94 (CH), 74.37 (CH), 56.05 (CH_2), 42.09 (CH), 35.85, 33.52, 28.92 (CH_2). IR (cm^{-1}): 3026, 2933, 2852, 1603, 1508, 1473, 1453, 1321, 1222, 1120, 823, 773, 747, 699. MALDI-MS ($C_{24}H_{24}FN$): $[MH]^+$ 346.1982 (calcd. 346.1971). Anal. Calcd for $C_{24}H_{24}FN$: C, 83.44; H, 7.00; N,

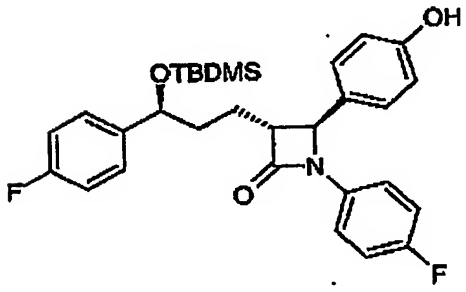
4.05. Found: C, 83.45; H, 7.06; N, 4.27.

Example 2



VI

a)



VIa

Ezetimibe (commercially obtained or synthesized according to Wu, G. Z. et al., *J. Org. Chem.* **1999**, *64*, 3714-3718) (5.530 g, 13.5 mmol) was suspended in 2-propanol (70 mL), aq. NaOH (2M, 15 mL) followed by Ac_2O (3.0 mL, 32 mmol) were added and the solution was stirred for 5 h followed by addition of sat. aq. $NaHCO_3$ (200 mL). After extraction with EtOAc (4 x 50 mL), the combined organic layer was washed successively with sat. aq. $NaHCO_3$ (50 mL) and H_2O (50 mL), evaporated on celite and purified by dry column vacuum chromatography (5.2 x 5.5 cm) on silica gel eluting with a gradient of 0-100% EtOAc in hexane (v/v) to give the corresponding azetidinone acetate (5.930 g, 97%) as a white foam.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.31 (2H, d, J = 8.7 Hz), 7.29-7.18

(4H, m), 7.09 (2H, d, J = 8.7 Hz), 6.99 (2H, t, J = 8.7 Hz), 6.92 (2H, t, J = 8.7 Hz), 4.67 (1H, bs), 4.61 (1H, d, J = 2.5 Hz), 3.08-3.04 (1H, m), 2.75 (1H, bs), 2.29 (3H, s), 1.97-1.85 (4H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 169.16, 167.23, 163.56, 160.46, 160.32, 157.24, 150.58, 139.94, 139.90, 134.85, 133.53, 133.50 (C), 127.32, 127.21, 126.78, 122.38, 118.34, 118.23, 115.95, 115.65, 115.35, 115.07 (CH), 72.95, 60.81, 60.33 (CH), 36.61, 25.07 (CH_2), 21.19 (CH_3). IR (cm^{-1}): 3443, 3019, 2936, 2862, 1747, 1605, 1509, 1427, 1388, 1370, 1221, 1198, 1157, 1016, 835, 757, 668. MALDI-MS ($C_{26}H_{23}F_2NO_4$): $[MH-H_2O]^+$ 434.1556 (calcd. 434.1568); $[MNa]^+$ 474.1485 (calcd. 474.1493))

Subsequently the acetate (1.864 g, 4.13 mmol) was dissolved in anhydrous DMF (25 mL), imidazole (939 mg, 13.8 mmol) and TBDMSCl (1.853 g, 12.3 mmol) were added sequentially and the solution was stirred for 3 h followed by addition of 50% sat. aq. $NaHCO_3$ (150 mL). After extraction with EtOAc (4 x 40 mL), the combined organic layer was washed successively with sat. aq. $NaHCO_3$ (40 mL) and H_2O (40 mL), evaporated on celite and purified by dry column vacuum chromatography (4.2 x 5.5 cm) on silica gel eluting with a gradient of 0-30% EtOAc in hexane (v/v) to give the corresponding silylated azetidinone acetate (2.137 g, 91%) as a colourless oil.

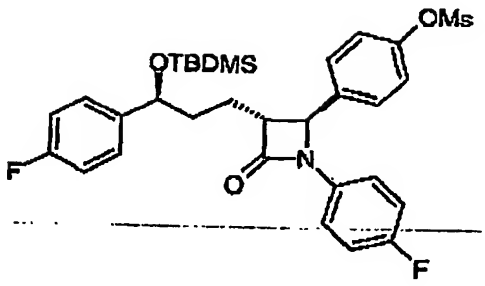
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.31 (2H, d, J = 8.7 Hz), 7.26-7.20 (4H, m), 7.10 (2H, d, J = 8.7 Hz), 6.98 (2H, t, J = 8.7 Hz), 6.91 (2H, t, J = 8.7 Hz), 4.67 (1H, t, J = 5.3 Hz), 4.58 (1H, d, J = 1.9 Hz), 3.06-3.02 (1H, m), 2.28 (3H, s), 1.96-1.80 (4H, m), 0.88 (9H, s), 0.02 (3H, s), -0.16 (3H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 169.16, 167.06, 163.42, 160.47, 160.16, 157.23, 150.62, 140.50, 135.10, 133.74, 133.70 (C), 127.26, 127.14, 126.77, 122.37, 118.27, 118.16, 115.89, 115.58, 115.03, 114.76 (CH), 73.74, 60.67, 60.53 (CH), 37.94 (CH_2), 25.73 (CH_3), 24.55 (CH_2), 20.99 (CH_3), 18.07 (C), -4.74, -5.05 (CH_3). IR (cm^{-1}): 2953, 2930, 2857, 1752, 1606, 1510, 1472, 1426, 1385, 1370, 1252, 1219,

1197, 1166, 1140, 1102, 1086, 1015, 912, 835, 777, 736. MALDI-MS: $[MH-TBDMSOH]^+$ 434.1556 (calcd. 434.1568); $[MNa]^+$ 588.2347 (calcd. 588.2358). Anal. Calcd for $C_{32}H_{37}F_2NO_4Si$: C, 67.94; H, 6.59; N, 2.48. Found: C, 67.94; H, 6.64; N, 2.37)

The silylated azetidinone acetate (5.123 g, 9.06 mmol) was dissolved in CH_2Cl_2 (200 mL), neutral alumina (50 g) was added and the suspension was evaporated to dryness. The coated alumina was dried shortly under vacuum and then heated to 70°C for 5.5 h. After cooling, the alumina was extracted with 10% MeOH in CH_2Cl_2 (8 x 50 mL) and the combined organic extracts were evaporated on celite and purified by dry column vacuum chromatography (5.4 x 5.5 cm) on silica gel eluting with a gradient of 0-30% EtOAc in hexane (v/v) to give the silylated azetidinone phenol **VIa** (3.919 g, 83%) as a white foam.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.26-7.14 (6H, m), 6.99-6.83 (6H, m), 6.16 (1H, bs), 4.65 (1H, t, J = 5.3 Hz), 4.52 (1H, d, J = 1.9 Hz), 3.04-2.98 (1H, m), 1.92-1.76 (4H, m), 0.86 (9H, s), 0.00 (3H, s), -0.17 (3H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.82, 163.28, 160.42, 156.12, 140.50, 140.45, 133.57 (C), 128.92, 127.19, 127.15, 127.08, 118.43, 118.32, 116.05, 115.85, 115.55, 115.01, 114.72 (CH), 73.82, 61.17, 60.35 (CH), 38.07 (CH_2), 25.89 (CH_3), 24.68 (CH_2), 18.25 (C), -4.54, -4.84 (CH_3). IR (cm^{-1}): 3351, 2953, 2938, 2857, 1722, 1615, 1604, 1510, 1450, 1391, 1361, 1252, 1223, 1156, 1103, 1087, 863, 834, 776, 760. MALDI-MS: $[MH-TBDMSOH]^+$ 392.1451 (calcd. 392.1462); $[MH]^+$ 524.2409 (calcd. 524.2433); $[MNa]^+$ 546.2242 (calcd. 546.2252). Anal. Calcd for $C_{30}H_{35}F_2NO_3Si$: C, 68.81; H, 6.74; N, 2.67. Found: C, 68.61; H, 6.82; N, 2.66.

b)



VIb

The silylated azetidinone phenol **VIa** (176 mg, 0.336 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL), anhydrous pyridine (0.5 mL) followed by MsCl (0.1 mL, 1.29 mmol) were added and the solution was stirred for 22 h, diluted with EtOAc (50 mL) and washed sequentially with sat. aq. $NaHCO_3$ (20 mL) and H_2O (20 mL). The organic layer was evaporated on celite and purified by dry column vacuum chromatography (4.2x3.3 cm) on silica gel eluting with a gradient of 0-50% EtOAc in hexane (v/v) to give the intermediate mesylate **VIb** (195.5 mg, 92%) as a colourless oil.

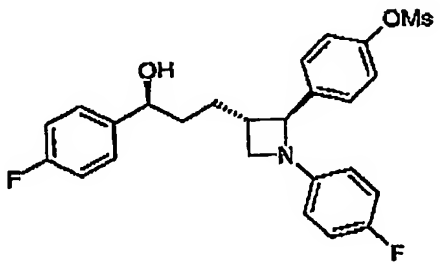
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.35 (2H, d, J = 8.7 Hz), 7.28 (2H, d, J = 8.7 Hz), 7.26-7.18 (4H, m), 6.98 (2H, t, J = 8.7 Hz), 6.93 (2H, t, J = 8.7 Hz), 4.67 (1H, dd, J = 4.4, 6.2 Hz), 4.59 (1H, d, J = 1.9 Hz), 3.16 (3H, s), 3.04-3.00 (1H, m), 1.93-1.79 (4H, m), 0.87 (9H, s), 0.01 (3H, s), -0.16 (3H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.83, 163.46, 160.57, 160.21, 157.34, 148.88, 140.53, 140.49, 137.07, 133.59, 133.56 (C), 127.36, 127.28, 127.18, 122.94, 118.26, 118.16, 116.04, 115.73, 115.10, 114.81 (CH), 73.79, 60.67, 60.41 (CH), 37.97 (CH_2), 37.59, 25.76 (CH_3), 24.60 (CH_2), 18.11 (C), -4.71, -5.02 (CH_3). IR (cm^{-1}): 2952, 2931, 2857, 1752, 1605, 1509, 1371, 1252, 1220, 1176, 1153, 1102, 1086, 971, 871, 835, 777. MALDI-MS: $[MH-TBDMSOH]^+$ 470.1228 (calcd. 470.12376); $[MNa]^+$ 624.2029 (calcd. 624.2027). Anal. Calcd for $C_{31}H_{37}F_2NO_5SiS$: C, 61.87; H, 6.20; N, 2.33. Found: C, 61.69; H, 6.19; N, 2.15).

c)

The intermediate mesylate received in the previous step (67.7 mg, 0.112 mmol) was dissolved in THF (2 mL), TBAF (0.2 mL, 1M in THF) was added and the solution was stirred for 1.5 h, diluted with EtOAc (20 mL) and washed successively with sat. aq. $NaHCO_3$ (10 mL) and H_2O (10 mL). The organic layer was evaporated on celite and purified by dry column vacuum chromatography (4.2 x 2.0 cm) on silica gel eluting with a gradient of 0-90% EtOAc in hexane (v/v) to give the desired mesylated azetidinone **VI** (37.0 mg, 68%) as a white solid after coevaporation with hexane (10 mL).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.37-7.17 (8H, m), 7.03-6.91 (4H, m), 4.69 (1H, t, J = 5.9 Hz), 4.65 (1H, d, J = 1.9 Hz), 3.16 (3H, s), 3.07-3.01 (1H, m), 2.63 (1H, bs), 2.03-1.84 (4H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.11, 163.76, 160.68, 160.50, 157.44, 148.89, 139.92, 136.86, 133.41 (C), 127.40, 127.27, 122.98, 118.35, 118.24, 116.10, 115.79, 115.45, 115.18, 115.11 (CH), 73.03, 60.48, 60.41 (CH), 37.63 (CH_3), 36.48, 25.00 (CH_2). IR (cm^{-1}): 3428, 2937, 1744, 1604, 1510, 1426, 1369, 1221, 1176, 1152, 1103, 1016, 971, 912, 872, 835, 788, 734. MALDI-MS: $[MH-H_2O]^+$ 470.1239 (calcd. 470.1238); $[MNa]^+$ 510.1164 (calcd. 510.1163). Anal. Calcd for $C_{25}H_{23}F_2NO_5S$: C, 61.59; H, 4.75; N, 2.87. Found: C, 61.79; H, 4.89; N, 2.76.

Example 3



VII

$LiAlH_4$ (58 mg, 1.5 mmol) and $AlCl_3$ (202 mg, 1.5 mmol) were suspended in anhydrous ether (15 mL), refluxed for 30 min and cooled to 0°C. The mesylate **VIb** obtained in step 2b) (195.5 mg, 0.325 mmol) dissolved in anhydrous ether (5 mL) was added and after stirring at 0°C for 15 min, sat. aq. $NaHCO_3$ (1 mL) was added dropwise. The suspension was evaporated on celite and purified by dry column vacuum chromatography (4.6 x 3.3 cm) on silica gel eluting with a gradient of 0-50% EtOAc in hexane (v/v) to give the intermediate silylated azetidine (146.4 mg, 77%) as a colourless oil.

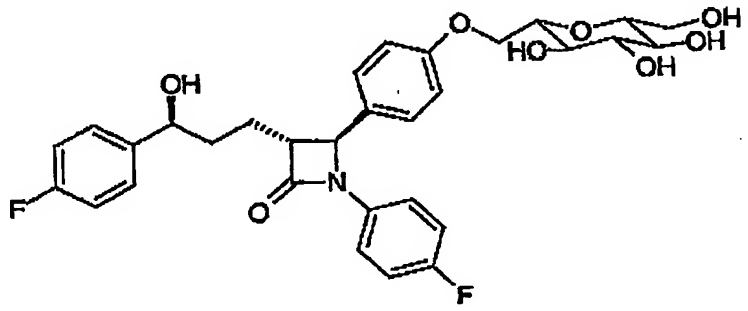
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.49 (2H, d, J = 8.7 Hz), 7.30 (2H, d, J = 8.7 Hz), 7.18 (2H, dd, J = 5.0, 8.7 Hz), 6.98 (2H, t, J = 8.7 Hz), 6.85 (2H, t, J = 8.7 Hz), 6.31 (2H, dd, J = 4.4, 9.3 Hz), 4.58 (1H, t, J = 5.3 Hz), 4.40 (1H, d, J = 6.8 Hz), 4.11 (1H, t, J = 7.2 Hz), 3.28 (1H, t, J = 7.2 Hz), 3.17 (3H, s), 2.56-2.49 (1H, m), 1.77-1.50 (4H, m), 0.88 (9H, s), 0.01 (3H, s), -0.15 (3H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 163.22, 159.99, 157.69, 154.57, 148.23, 148.07, 141.97, 140.62 (C), 127.41, 127.13, 127.03, 122.25, 115.43, 115.13, 114.96, 114.68, 113.00, 112.90 (CH), 73.86, 73.29 (CH), 55.88 (CH_2), 41.88 (CH), 37.90 (CH_2), 37.43 (CH_3), 29.43 (CH_2), 25.85 (CH_3), 18.24 (C), -4.53, -4.88 (CH_3). IR (cm^{-1}): 2932, 2856, 1605, 1509, 1473, 1372, 1331, 1252, 1222, 1198, 1171, 1151, 1090, 970, 870, 836, 776. MALDI-MS: $[MH-TBDMSOH]^+$ 456.1442 (calcd. 456.14449); $[MNa]^+$ 610.2236 (calcd. 610.22348). Anal. Calcd for $C_{31}H_{39}F_2NO_4SiS$: C, 63.34; H, 6.69; N, 2.38. Found: C, 63.49; H, 6.87; N, 2.33.

This intermediate silylated azetidine (146.3 mg, 0.249 mmol) was dissolved in anhydrous THF (5.0 mL, teflon bottle) at 0°C, anhydrous pyridine (1.0 mL) followed by HF-pyridine complex (1.0 mL) were added and the solution was stirred at 0°C for 1 h and at room temperature for 7 h, diluted with ether (30 mL) and washed with sat. aq. $NaHCO_3$ (3 x 10 mL). The organic layer was evapo-

rated on celite and purified by dry column vacuum chromatography (4.2 x 2.0 cm) on silica gel eluting with a gradient of 0-90% EtOAc in hexane (v/v) to give the desired mesylated azetidine **VII** (100.0 mg, 85%) as a white foam.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.50 (2H, d, J = 8.7 Hz), 7.28 (2H, d, J = 8.7 Hz), 7.22 (2H, dd, J = 5.6, 8.7 Hz), 7.01 (2H, t, J = 8.7 Hz), 6.84 (2H, t, J = 8.7 Hz), 6.30 (2H, dd, J = 4.3, 9.3 Hz), 4.57 (1H, t, J = 5.6 Hz), 4.41 (1H, d, J = 6.8 Hz), 4.12 (1H, t, J = 6.8 Hz), 3.30 (1H, dd, J = 6.8, 7.5 Hz), 3.16 (3H, s), 2.55 (1H, dt, J = 6.8, 7.5 Hz), 1.93 (1H, bs), 1.88-1.53 (4H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 163.62, 160.37, 157.74, 154.61, 148.22, 148.01, 141.89, 139.95, 139.91 (C), 127.46, 127.28, 127.17, 122.29, 115.46, 115.42, 115.13, 113.02, 112.92 (CH), 73.43, 73.28 (CH), 55.92 (CH_2), 41.81 (CH), 37.49 (CH_3), 36.28, 29.85 (CH_2). IR (cm^{-1}): 3416, 2938, 2853, 1508, 1367, 1221, 1196, 1171, 1149, 970, 871, 823. MALDI-MS ($C_{25}H_{25}F_2NO_4S$): $[MH-H_2O]^+$ 456.1447 (calcd. 456.1445); $[M]^+$ 473.1481 (calcd. 473.1472); $[MNa]^+$ 496.1380 (calcd. 496.1370).

Example 4



VIII

The silylated azetidinone phenol **VIa** obtained in step 2a) (143 mg, 0.273 mmol) and C-(hydroxymethyl)-2,3,4,6-tetra-*O*-benzyl-β-D-

glucopyranoside (prepared according to RajanBabu, T. V. and Reddy, G. S. *J. Org. Chem.* **1986**, *51*, 5458-5461; 180 mg, 0.325 mmol) were dissolved in anhydrous THF (10 mL) at 0°C, Bu_3P (0.20 mL, 0.80 mmol) and 1,1'-(azodicarbonyl)dipiperdine (206 mg, 0.82 mmol) were added sequentially and the suspension was allowed to warm to ambient temperature over several hours and stirred for 24 h. EtOAc/hexane (1:4 (v/v), 20 mL) was added, the suspension was filtered through celite (2 x 10 mL EtOAc/hexane (1:4 (v/v)) washings) and the filtrate was evaporated on celite and purified by dry column vacuum chromatography (4.1 x 3.3 cm) on silica gel eluting with a gradient of 0-50% EtOAc in hexane (v/v) to give the corresponding *C*-glycoside (60.1 mg, 21%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.37-7.17 (26H, m), 7.04-6.89 (6H, m), 4.96 (2H, bs), 4.89 (1H, d, J = 9.3 Hz), 4.86 (1H, d, J = 8.7 Hz), 4.69 (1H, t, J = 5.3 Hz), 4.63-4.53 (5H, m), 4.21 (1H, d, J = 10.6 Hz), 4.10 (1H, dd, J = 5.0, 10.6 Hz), 3.85-3.52 (7H, m), 3.07-3.02 (1H, m), 2.01-1.78 (4H, m), 0.91 (9H, s), 0.05 (3H, s), -0.13 (3H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.25, 158.74, 140.53, 140.49, 138.29, 137.85, 137.79, 137.65, 133.81 (C), 129.53, 128.32, 128.28, 128.18, 127.96, 127.81, 127.78, 127.74, 127.66, 127.54, 127.48, 127.18, 127.08, 126.90, 118.22, 118.12, 115.77, 115.47, 115.30, 114.98, 114.70 (CH), 87.12, 79.14, 78.25, 77.87, 77.71 (CH), 75.56, 75.11, 75.03 (CH_2), 73.82 (CH), 73.44, 68.93, 67.23 (CH_2), 61.02, 60.47 (CH), 38.10 (CH_2), 25.89 (CH_3), 24.71 (CH_2), 18.24 (C), -4.54, -4.83 (CH_3). IR (cm^{-1}): 2951, 2929, 2858, 1749, 1608, 1510, 1454, 1386, 1361, 1250, 1223, 1156, 1141, 1101, 1028, 911, 835, 777, 735, 699. MALDI-MS ($C_{65}H_{71}F_2NO_8Si$): $[MNa]^+$ 1082.4831 (calcd. 1082.4815).

This *C*-Glycoside (72 mg, 0.068 mmol) was subsequently dissolved in EtOH (5 mL), $Pd(OH)_2/C$ (20% (w/w), 40 mg) was added and the suspension was evacuated 4 times with H_2 and stirred under an H_2-atmosphere for 17 h. The suspension was evaporated on celite and

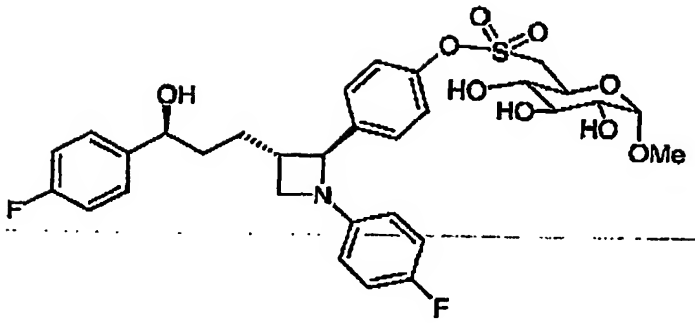
purified by dry column vacuum chromatography (3.8 x 2.0 cm) on silica gel eluting with a gradient of 0-100% EtOAc in hexane followed by 10% MeOH in CH_2Cl_2 (v/v) to give the debenzylated *C*-glycoside (28 mg, 59%) as colourless oil.

^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.22, 163.28, 160.05, 158.36, 157.03, 140.57, 133.75, 130.30, 129.52, 127.22, 127.11, 118.23, 115.83, 115.54, 116.35, 115.05, 114.91, 114.76, 79.16, 78.33, 77.70, 73.88, 70.18, 69.52, 67.75, 61.54, 60.79, 60.57, 38.14, 25.91, 24.81, 18.27, -4.51, -4.80. IR (cm^{-1}): 3391, 2930, 2858, 1747, 1609, 1510, 1387, 1362, 1223, 1140, 1086, 1043, 1014, 835, 758. MALDI-MS ($C_{37}H_{47}F_2NO_8Si$): $[MH-TBDMSOH]^+$ 568.2132 (calcd. 568.2147); $[MNa]^+$ 722.2939 (calcd. 722.2937).

Subsequently , the debenzylated C-Glycoside (27.0 mg, 0.039 mmol) was dissolved in THF (1.0 mL), TBAF (0.2 mL, 1M in THF) was added and the solution was stirred for 15 h, diluted with CH_2Cl_2, evaporated on celite and purified by dry column vacuum chromatography (3.5 x 2.0 cm) on silica gel eluting with a gradient of 0-18% MeOH in CH_2Cl_2 (v/v) to give the desired *C*-glycoside **VIII** (14.0 mg, 62%) as a white solid after coevaporation with hexane (10 mL).

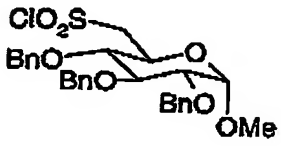
^{1}H-NMR (300 MHz, CD_3OD) δ: 7.33-7.23 (6H, m), 7.05-6.94 (6H, m), 4.78 (1H, d, J = 1.9 Hz), 4.59 (1H, t, J = 5.3 Hz), 4.29 (1H, dd, J = 1.5, 10.3 Hz), 4.13 (1H, dd, J = 5.6, 10.6 Hz), 3.85 (1H, d, J = 11.2 Hz), 3.67-3.61 (1H, m), 3.57-3.51 (1H, m), 3.44-3.37 (2H, m), 3.31-3.28 (2H, m), 3.11-3.06 (1H, m), 1.97-1.81 (4H, m). ^{13}C-NMR (75 MHz, CD_3OD) δ: 169.20, 160.12, 130.69, 128.36, 128.25, 128.14, 119.52, 119.41, 116.35, 116.04, 115.93, 115.63, 115.35, 81.55, 79.49, 79.39, 73.35, 71.30, 71.23, 68.77, 62.66, 61.74, 60.86, 37.22, 25.84. MALDI-MS ($C_{31}H_{33}F_2NO_8$): $[MH-TBDMSOH]^+$ 568.2143 (calcd. 568.2147); $[MNa]^+$ 608.2073 (calcd. 608.2072).

Example 5



IX

a)



IXa

Methyl 2,3,4-Tri-*O*-benzyl-α-D-glucopyranoside (prepared according to Jaramillo, C. et al; Chiara, J. L.; Martinlomas, M. *J. Org. Chem.* **1994**, *59*, 3135-3141; 1.181 g, 2.54 mmol) was dissolved in anhydrous CH_2Cl_2 (25 mL) at 0°C, anhydrous pyridine (3.0 mL) followed by MsCl (0.50 mL, 6.4 mmol) were added and the solution was stirred at 0°C for 1 h and at room temperature for 7 h followed by addition of sat. aq. $NaHCO_3$ (50 mL). The layers were separated and the aqueous layer extracted with EtOAc (3 x 25 mL). The combined organic layer was washed successively with sat. aq. $NaHCO_3$ (25 mL) and H_2O (25 mL), evaporated on celite and purified by dry column vacuum chromatography (4.1 x 3.3 cm) on silica gel eluting with a gradient of 0-100% CH_2Cl_2 in hexane (v/v) followed by 0.25-1.0% MeOH in CH_2Cl_2 (v/v) to give the corresponding mesylate (1.303 g, 94%) as a colourless oil after coevaporation with acetonitrile (3 x 10 mL).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.39-7.26 (15H, m), 5.02 (1H, d, J = 10.6 Hz), 4.92 (1H, d, J = 10.6 Hz), 4.84 (1H, d, J = 10.6 Hz), 4.80 (1H, d, J = 12.5 Hz), 4.66 (1H, d, J = 11.8 Hz), 4.63 (1H, d, J = 10.6 Hz), 4.60 (1H, d, J = 3.7 Hz), 4.41-4.32 (2H, m), 4.02 (1H, t, J = 9.3 Hz), 3.85 (1H, dt, J = 3.7, 10.0Hz), 3.52 (1H, dt, J = 3.7, 6.2 Hz), 3.50 (1H, bs), 3.39 (3H, s), 2.98 (3H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 138.30, 137.75, 137.56 (C), 128.36, 128.30, 127.94, 127.84, 127.76, 127.57 (CH), 98.06, 81.73, 79.69, 76.86 (CH), 75.73, 75.09, 73.44 (CH_2), 68.59 (CH), 68.36 (CH_2), 55.46, 37.54 (CH_3). IR (cm^{-1}): 3031, 2913, 1497, 1454, 1359, 1177, 1089, 1074, 1046, 1003, 965, 931, 813, 739, 699. MALDI-MS: $[MNa]^+$ 565.1873 (calcd. 565.1872). Anal. Calcd for $C_{29}H_{34}O_8S$: C, 64.19; H, 6.32. Found: C, 63.99; H, 6.27.

Subsequently, this mesylate (1.290 g, 2.38 mmol) was dissolved in EtOH (25 mL), KOSCMe (869 mg, 7.61 mmol) was added and the unclear solution was stirred at reflux for 4 h (orange precipitate). After cooling, 50% sat. aq. $NaHCO_3$ (100 mL) was added and the suspension was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed successively with sat. aq. $NaHCO_3$ (50 mL) and H_2O (50 mL), evaporated on celite and purified by dry column vacuum chromatography (4.1 x 3.3 cm) on silica gel eluting with a gradient of 0-30% EtOAc in hexane (v/v) to give the corresponding thioacetate (1.189 g, 96%) as a light orange solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.41-7.32 (15H, m), 5.03 (1H, d, J = 10.6 Hz), 4.94 (1H, d, J = 10.6 Hz), 4.86 (1H, d, J = 10.6 Hz), 4.82 (1H, d, J = 11.8 Hz), 4.69 (1H, d, J = 11.8 Hz), 4.66 (1H, d, J = 10.6 Hz), 4.58 (1H, d, J = 3.1 Hz), 4.02 (1H, t, J = 9.0 Hz), 3.81 (1H, dt, J = 2.5, 7.5 Hz), 3.55 (1H, dd, J = 3.7, 9.3 Hz), 3.48 (1H, dd, J = 3.1, 13.7 Hz), 3.40 (3H, s), 3.35 (1H, t, J = 9.5 Hz), 3.08 (1H, dd, J = 7.5, 13.7 Hz), 2.36 (3H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 194.67, 138.46, 137.90, 137.78 (C), 128.33, 128.29, 128.03, 127.94, 127.85, 127.81, 127.74, 127.53

(CH), 97.72, 81.69, 80.36, 79.78 (CH), 75.64, 75.04, 73.22 (CH_2), 69.23 (CH), 55.02 (CH_3), 30.73 (CH_2), 30.39 (CH_3). IR (cm^{-1}): 3063, 3031, 2908, 1694, 1497, 1454, 1358, 1201, 1156, 1136, 1092, 1072, 1050, 1029, 999, 955, 737, 698, 630. MALDI-MS: $[MNa]^+$ 545.1974 (calcd. 545.1974). Anal. Calcd for $C_{30}H_{34}O_6S$: C, 68.94; H, 6.56. Found: C, 68.77; H, 6.63.

The thioacetate received above (1.180 g, 2.26 mmol) was then dissolved in AcOH (25 mL), KOAc (4.082 g, 41.6 mmol) followed by Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, 4.019 g, 8.69 mmol) were added and after stirring for 15 h, sat. aq. $NaHCO_3$ (100 mL), H_2O (50 mL) and sat. aq. Na_2CO_3 (50 mL) were carefully added. After extraction with EtOAc (4 x 40 mL), the combined organic layer was washed with sat. aq. Na_2CO_3 (50 mL), evaporated on celite and purified by dry column vacuum chromatography (4.0 x 3.3 cm) on silica gel eluting with a gradient of 0-90% EtOAc in hexane (v/v) followed by 0-50% MeOH in EtOAc (v/v) to give the corresponding sulfonate salt (1.116 g, 90%) as a white solid.

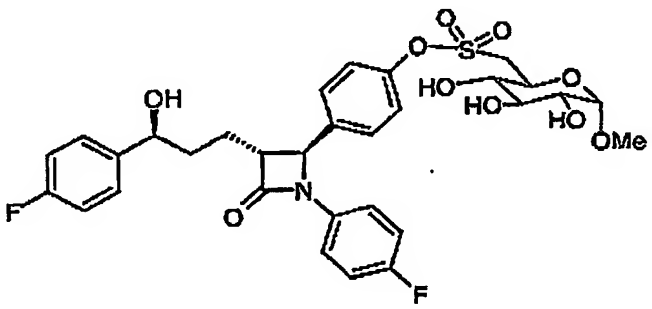
^{1}H-NMR (300 MHz, CD_3OD) δ: 7.37-7.21 (15H, m), 4.90 (1H, d, J = 11.2 Hz), 4.86 (1H, d, J = 10.6 Hz), 4.84 (1H, d, J = 11.2 Hz), 4.73 (1H, d, J = 3.1 Hz), 4.72 (1H, d, J = 11.2 Hz), 4.64 (1H, d, J = 12.5 Hz), 4.60 (1H, d, J = 11.2 Hz), 4.16 (1H, t, J = 9.2 Hz), 3.90 (1H, t, J = 9.3 Hz), 3.55 (1H, dd, J = 3.4, 9.3 Hz), 3.48 (3H, s), 3.30-3.22 (2H, m), 2.92 (1H, dd, J = 10.0, 14.3 Hz). ^{13}C-NMR (75 MHz, CD_3OD) δ: 140.03, 139.57, 139.55 (C), 129.42, 129.31, 129.15, 128.93, 128.89, 128.84, 128.67, 128.59 (CH), 98.53, 83.03, 81.65, 81.52 (CH), 76.44, 75.83, 73.85 (CH_2), 68.52 (CH), 55.95 (CH_3), 53.65 (CH_2). IR (cm^{-1}): 3484, 3030, 2922, 1497, 1454, 1360, 1230, 1198, 1177, 1156, 1093, 1058, 1028, 736, 696. MALDI-MS ($C_{28}H_{31}NaO_8S$): $[MNa]^+$ 573.1536 (calcd. 573.1535).

Finally, the obtained sulfonate salt (696 mg, 1.26 mmol) was suspended in anhydrous acetonitrile/CH_2Cl_2 (10 mL, 1:1 (v/v)) at 0°C, Ph_3P (1.002 g, 3.8 mmol) and thionyl chloride (0.40 mL, 5.5

mmol) were added sequentially and the suspension was stirred at room temperature for 13 h. EtOAc/hexane (1:4 (v/v), 100 mL) was added, the suspension was filtered through celite (4 x 15 mL EtOAc/hexane (1:3 (v/v)) washings) and the filtrate was evaporated and dried shortly under vacuum to give the desired sulfonyl chloride **IXa** (657 mg, 95%) as a yellowish oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.42-7.28 (15H, m), 5.05 (1H, d, J = 10.6 Hz), 4.96 (1H, d, J = 11.8 Hz), 4.85 (1H, d, J = 10.6 Hz), 4.83 (1H, d, J = 11.8 Hz), 4.67 (1H, d, J = 12.5 Hz), 4.60 (1H, d, J = 11.2 Hz), 4.60 (1H, d, J = 3.1 Hz), 4.33 (1H, t, J = 9.6 Hz), 4.07 (1H, t, J = 9.0 Hz), 3.85 (1H, dd, J = 1.2, 13.7 Hz), 3.55 (1H, d, J = 9.3 Hz), 3.52 (1H, t, J = 10.0 Hz), 3.46 (3H, s), 3.26 (1H, t, J = 9.5 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 138.02, 137.57, 137.06 (C), 128.58, 128.36, 128.30, 128.23, 128.12, 127.92, 127.66 (CH), 98.00, 81.56, 79.41, 78.49 (CH), 75.85, 74.76, 73.38, 66.75 (CH_2), 65.93 (CH), 55.90 (CH_3). MALDI-MS ($C_{28}H_{31}ClO_7S$): $[MNa]^+$ 569.1378 (calcd. 569.1377).

b)



IXb

The sulfonyl chloride **IXa** obtained in step 5a) (197 mg, 0.36 mmol) was suspended in anhydrous CH_2Cl_2 (5 mL), anhydrous pyri-

dine (0.5 mL) followed by the silylated azetidinone phenol **VIa** obtained in step 2a) (70.0 mg, 0.13 mmol) were added and the solution was stirred for 22 h, diluted with EtOAc (25 mL) and washed sequentially with sat. aq. $NaHCO_3$ (10 mL) and H_2O (10 mL). The organic layer was evaporated on celite and purified by dry column vacuum chromatography (4.3 x 2.0 cm) on silica gel eluting with a gradient of 0-35% EtOAc in hexane (v/v) to give the corresponding glycosylated azetidinone (125.5 mg, 91%) as a colourless oil/glass.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.37-7.14 (23H, m), 7.00 (2H, t, J = 8.7 Hz), 6.95 (2H, t, J = 8.7 Hz), 5.05 (1H, d, J = 11.2 Hz), 4.97 (1H, d, J = 11.2 Hz), 4.84 (1H, d, J = 11.8 Hz), 4.82 (1H, d, J = 10.6 Hz), 4.69 (1H, t, J = 6.8 Hz), 4.67 (1H, d, J = 12.5 Hz), 4.60 (1H, d, J = 3.7 Hz), 4.56 (1H, d, J = 12.5 Hz), 4.54 (1H, d, J = 10.6 Hz), 4.29 (1H, t, J = 9.5 Hz), 4.06 (1H, t, J = 9.0 Hz), 3.57 (1H, t, J = 3.1 Hz), 3.53 (1H, d, J = 3.1 Hz), 3.46 (3H, s), 3.26 (1H, t, J = 9.3 Hz), 3.14 (1H, dd, J = 10.0, 14.3 Hz), 2.96 (1H, dt, J = 1.9, 6.8 Hz), 1.97-1.78 (4H, m), 0.90 (9H, s), 0.04 (3H, s), -0.13 (3H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.62, 163.27, 160.37, 160.03, 157.14, 148.91, 140.33, 138.05, 137.63, 137.29, 136.67, 133.45, 133.42 (C), 128.44, 128.31, 128.18, 128.04, 127.96, 127.86, 127.65, 127.15, 127.03, 126.97, 123.15, 118.13, 118.03, 115.93, 115.64, 115.02, 114.75 (CH), 97.92, 81.67, 79.60, 79.23 (CH), 75.78, 74.86 (CH_2), 73.78 (CH), 73.37 (CH_2), 65.64, 60.66, 60.48 (CH), 55.73 (CH_3), 51.63, 38.06 (CH_2), 25.85 (CH_3), 24.69 (CH_2), 18.22 (C), -4.54, -4.87 (CH_3). IR (cm^{-1}): 3032, 2930, 2858, 1750, 1605, 1510, 1455, 1386, 1252, 1220, 1153, 1086, 1073, 1048, 870, 836, 755, 699. MALDI-MS: $[MNa]^+$ 1056.3969 (calcd. 1056.3964). Anal. Calcd for $C_{58}H_{65}F_2NO_{10}SiS$: C, 67.35; H, 6.33; N, 1.35. Found: C, 67.43; H, 6.44; N, 1.33.

Subsequently the glycosylated azetidinone (105.1 mg, 0.102 mmol) was dissolved in EtOH (5 mL), $Pd(OH)_2/C$ (20% (w/w), 33 mg) was

added and the suspension was evacuated 4 times with H_2 and stirred under an H_2-atmosphere for 6 h. The suspension was evaporated on celite and purified by dry column vacuum chromatography (4.2 x 2.0 cm) on silica gel eluting with a gradient of 0-10% MeOH in CH_2Cl_2 (v/v) to give the debenzylated azetidinone (63.2 mg, 81%) as a colourless oil.

^{1}H-NMR (300 MHz, acetone-d_6) δ: 7.55 (2H, d, J = 8.7 Hz), 7.42 (2H, d, J = 8.7 Hz), 7.37 (2H, dd, J = 5.9, 8.4 Hz), 7.28 (2H, dd, J = 5.0, 9.3 Hz), 7.11-7.01 (4H, m), 4.96 (1H, d, J = 1.9 Hz), 4.84 (1H, t, J= 5.3 Hz), 4.69 (1H, d, J = 3.7 Hz), 4.61 (1H, d, J = 5.0 Hz), 4.35 (1H, d, J = 3.1 Hz), 4.16 (1H, dt, J = 1.2, 10.0 Hz), 3.87 (1H, dd, J = 1.2, 14.9 Hz), 3.79 (1H, d, J = 7.5 Hz), 3.65 (1H, t, J = 9.0 Hz), 3.56 (1H, dd, J = 10.0, 14.9 Hz), 3.45-3.40 (1H, m), 3.38 (3H, s), 3.27-3.14 (2H, m), 2.00-1.88 (4H, m), 0.87 (9H, s), 0.05 (3H, s), -0.15 (3H, s). ^{13}C-NMR (75 MHz, acetone-d_6) δ: 167.25, 163.96, 160.84, 160.75, 157.65, 150.14, 141.91, 141.87, 138.13, 134.95, 134.91 (C), 128.32, 128.23, 123.84, 118.98, 118.88, 116.43, 116.12, 115.49, 115.21 (CH), 100.74, 74.77, 74.42, 73.55, 73.04, 68.01, 61.25, 60.50 (CH), 55.56 (CH_3), 52.83, 38.50 (CH_2), 26.16 (CH_3), 25.34 (CH_2), 18.65 (C), -4.47, -4.71 (CH_3). IR (cm^{-1}): 3396, 2951, 2931, 2857, 1754, 1701, 1605, 1510, 1426, 1385, 1250, 1220, 1151, 1103, 1088, 1053, 1015, 988, 872, 836, 778. MALDI-MS ($C_{37}H_{47}F_2NO_{10}SSi$): $[MNa]^+$ 786.2559 (calcd. 786.2556).

This debenzylated azetidinone (58.9 mg, 0.077 mmol) was dissolved in anhydrous THF (2.5 mL, teflon bottle), anhydrous pyridine (0.5 mL) followed by HF·pyridine complex (0.5 mL) were added and the solution was stirred for 14.5 h, diluted with ether (20 mL) and washed with sat. aq. $NaHCO_3$ (3 x 5 mL). The organic layer was evaporated on celite and purified by dry column vacuum chromatography (4.2 x 2.0 cm) on silica gel eluting with a gradient of 0-10% MeOH in CH_2Cl_2 (v/v) to give the desired azetidinone **IXb** (44.9 mg, 90%) as a white solid.

^{1}H-NMR (300 MHz, acetone-d_6) δ: 7.56 (2H, d, J = 8.7 Hz), 7.43 (2H, d, J = 8.7 Hz), 7.37 (2H, dd, J = 5.6, 8.7 Hz), 7.30 (2H, dd, J = 4.7, 9.0 Hz), 7.06 (2H, d, J = 9.3 Hz), 7.03 (2H, d, J = 8.7 Hz), 4.99 (1H, d, J = 2.5 Hz), 4.69 (1H, d, J = 3.7 Hz), 4.61 (1H, d, J= 5.0 Hz), 4.42 (1H, d, J = 3.7 Hz), 4.34 (1H, bs), 4.15 (1H, dt, J = 1.2, 8.7 Hz), 3.86 (1H, dd, J = 1.2, 14.9 Hz), 3.79 (1H, d, J = 8.1 Hz), 3.65 (1H, t, J = 8.7 Hz), 3.57 (1H, dd, J = 10.0, 14.9 Hz), 3.44-3.38 (1H, m), 3.38 (3H, s), 3.32-3.14 (2H, m), 2.08-1.86 (4H, m). ^{13}C-NMR (75 MHz, acetone-d_6) δ: 167.42, 163.87, 160.85, 157.67, 150.13, 142.52, 138.18, 134.93 (C), 128.35, 128.22, 128.13, 123.83, 119.01, 118.89, 116.44, 116.13, 115.40, 115.11 (CH), 100.74, 74.77, 73.56, 73.04, 72.77, 68.01, 61.27, 60.56 (CH), 55.56 (CH_3), 52.83, 37.54, 25.70 (CH_2). IR (cm^{-1}): 3395, 2925, 1732, 1604, 1509, 1365, 1219, 1148, 1103, 1051, 1014, 871, 834, 752. MALDI-MS: $[MNa]^+$ 672.1693 (calcd. 672.1691). Anal. Calcd for $C_{31}H_{33}F_2NO_{10}S$: C, 57.31; H, 5.12; N, 2.16. Found: C, 57.34; H, 5.26; N, 2.21.

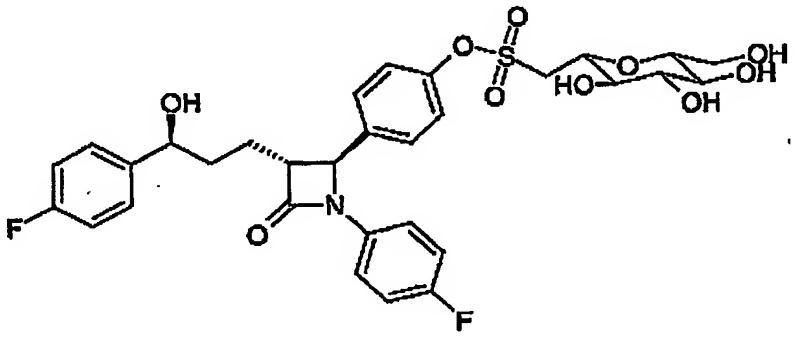
c)

$LiAlH_4$ (57 mg, 1.5 mmol) and $AlCl_3$ (200 mg, 1.5 mmol) were suspended in anhydrous ether (15 mL), refluxed for 30 min and cooled to 0°C. The azetidinone **IXb** obtained under step 5b) (26.8 mg, 0.041 mmol) dissolved in anhydrous THF (1 mL, 2 x 0.5 mL rinse) was added and after stirring at 0°C for 10 min, sat. aq. $NaHCO_3$ (1 mL) was added dropwise. The suspension was evaporated on celite and purified by dry column vacuum chromatography (4.7 x 2.0 cm) on silica gel eluting with a gradient of 0-12% MeOH in CH_2Cl_2 (v/v) to give the desired azetidine **IX** (20.4 mg, 78%) as a colourless oil.

^{1}H-NMR (300 MHz, acetone-d_6) δ: 7.63-7.59 (2H, m), 7.49-7.42 (2H, m), 7.36-7.29 (2H, m), 7.10-7.01 (2H, m), 6.92-6.77 (2H, m), 6.40-6.35 (2H, m), 4.72 (1H, d, J = 3.7 Hz), 4.62 (1H, d, J = 5.0 Hz), 4.61 (1H, bs), 4.52 (1H, d, J = 6.9 Hz), 4.31 (2H, t, J

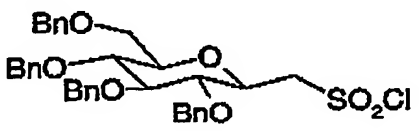
= 4.4 Hz), 4.21-4.15 (2H, m), 3.90 (1H, dd, J = 1.2, 14.9 Hz), 3.76 (1H, d, J = 8.1 Hz), 3.68 (1H, dd, J = 3.7, 9.3 Hz), 3.66-3.57 (2H, m), 3.41 (3H, s, OMe), 3.38-3.31 (1H, m), 3.25 (1H, dt, J = 5.0, 13.7 Hz), 2.62 (1H, dd, J = 6.8, 14.3 Hz), 1.92-1.84 (1H, m), 1.74-1.57 (3H, m). ^{13}C-NMR (75 MHz, acetone-d_6) δ: 163.90, 160.69, 158.31, 155.22, 149.93, 149.72, 149.52, 142.90, 142.84 (C), 129.60, 129.44, 128.30, 128.24, 128.13, 123.51, 122.99, 115.95, 115.91, 115.66, 115.40, 115.11, 113.87, 113.77, 113.67, 113.57 (CH), 100.84, 74.86, 74.03, 73.68, 73.14, 72.87, 68.09 (CH), 56.67 (CH_2), 55.63 (CH_3), 52.83 (CH_2), 42.78 (CH), 37.60, 29.83 (CH_2). IR (cm^{-1}): 3390, 2935, 2850, 1605, 1508, 1474, 1366, 1221, 1147, 1052, 1015, 874, 824, 755. MALDI-MS ($C_{31}H_{35}F_2NO_9S$): $[MH-H_2O]^+$ 618.1968 (calcd. 618.1973); $[MH]^+$ 636.2045 (calcd. 636.2079); $[MNa]^+$ 658.1901 (calcd. 658.1898).

Example 6



x

a)



xa

The above sulfonyl chloride **Xa** was prepared according to the methods described under step 5a) using *C*-(Hydroxymethyl)-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside (prepared according to RajanBabu, T. V.; Reddy, G. S. *J. Org. Chem.* **1986**, *51*, 5458-5461) as the starting material.

b)

The sulfonyl chloride **Xa** obtained under step 6a) (871 mg, 1.26 mmol) was suspended in anhydrous CH_2Cl_2 (10 mL), anhydrous pyridine (1.0 mL) followed by the silylated azetidinone phenol **VIa** obtained in step 2a) (334 mg, 0.634 mmol) were added and the solution was stirred for 13 h, diluted with EtOAc (50 mL) and washed sequentially with sat. aq. $NaHCO_3$ (20 mL) and H_2O (20 mL). The organic layer was evaporated on celite and purified by dry column vacuum chromatography (4.3 x 3.3 cm) on silica gel eluting with a gradient of 0-100% CH_2Cl_2 in hexane (v/v) to give the corresponding glycosylated azetidinone (657 mg, 92%) as a white foam.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.37-7.15 (28H, m), 7.01 (2H, t, *J* = 8.7 Hz), 6.96 (2H, t, *J* = 8.7 Hz), 5.03-4.81 (4H, m), 4.73-4.51 (6H, m), 3.95 (1H, t, *J* = 8.4 Hz), 3.78 (4H, bs), 3.57-3.53 (1H, m), 3.48 (1H, d, *J* = 1.2 Hz), 3.40 (1H, t, *J* = 9.0 Hz), 3.24 (1H, dd, *J* = 9.3, 14.9 Hz), 3.02-2.95 (1H, m), 1.97-1.80 (4H, m), 0.92 (9H, s), 0.06 (3H, s), -0.11 (3H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 166.72, 163.24, 160.35, 160.01, 157.13, 149.25, 140.37, 140.33, 137.90, 137.65, 137.58, 137.12, 136.97, 136.52, 133.52, 133.48 (C), 128.46, 128.32, 128.28, 128.17, 128.02, 127.97, 127.81, 127.76, 127.67, 127.63, 127.52, 127.13, 127.02, 123.32, 118.13, 118.02, 115.90, 115.60, 115.01, 114.72 (CH), 86.83, 79.13, 78.83, 77.73 (CH), 75.56, 75.00, 74.85 (CH_2), 74.19, 73.77 (CH), 73.31 (CH_2), 68.36, 60.57, 60.53 (CH), 51.31, 38.03 (CH_2), 25.85 (CH_3), 24.67 (CH_2), 18.20 (C), -4.57, -4.87 (CH_3). IR (cm^{-1}): 2951, 2929, 2858, 1751, 1605, 1510, 1454, 1386, 1362, 1251,

1220, 1151, 1102, 871, 835, 776, 754, 699. MALDI-MS: $[MNa]^+$ 1146.4440 (calcd. 1146.4434). Anal. Calcd for $C_{65}H_{71}F_2NO_{10}SiS$: C, 69.43; H, 6.36; N, 1.25. Found: C, 69.27; H, 6.47; N, 1.28.

The glycosylated azetidinone obtained above (236 mg, 0.210 mmol) was then dissolved in EtOH/EtOAc (10 mL, 1:1 (v/v)), $Pd(OH)_2/C$ (20% (w/w), 73 mg) was added and the suspension was evacuated 4 times with H_2 and stirred under an H_2-atmosphere for 3.5 h. The suspension was evaporated on celite and purified by dry column vacuum chromatography (4.6 x 2.0 cm) on silica gel eluting with a gradient of 0-20% MeOH in CH_2Cl_2 (v/v) to give the debenzylated azetidinone (145 mg, 90%) as a white foam.

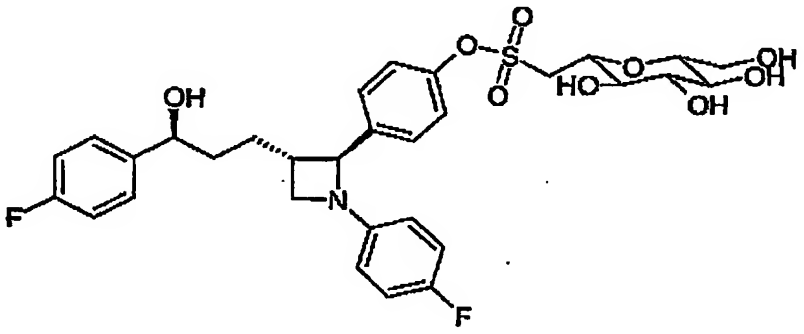
^{1}H-NMR (300 MHz, acetone-d_6) δ: 7.55 (2H, dd, J = 6.5, 8.7 Hz), 7.47 (2H, d, J = 8.4 Hz), 7.40-7.20 (4H, m), 7.11-6.98 (4H, m), 4.97 (1H, dd, J = 2.3, 10.5 Hz), 4.83 (1H, bs), 4.61 (1H, bs), 4.48 (1H, bs), 4.30 (1H, bs), 3.90-3.81 (3H, m), 3.71-3.64 (1H, m), 3.56-3.38 (5H, m), 3.25-3.14 (2H, m), 2.66 (1H, t, J = 7.2 Hz), 1.98-1.81 (4H, m), 0.88 (9H, s), 0.05 (3H, s), -0.15 (3H, s). ^{13}C-NMR (75 MHz, acetone-d_6) δ: 168.30, 161.88, 158.69, 151.25, 142.96, 139.63, 139.16, 139.13, 135.98 (C), 131.66, 131.56, 129.36, 129.28, 124.92, 120.00, 119.90, 117.46, 117.16, 116.62, 116.52 (CH), 82.13, 80.16, 76.75, 75.44, 74.46, 72.35 (CH), 63.64 (CH_2), 61.60, 61.55 (CH), 54.03, 39.52 (CH_2), 27.20 (CH_3), 26.35 (CH_2), 19.68 (C), -3.44, -3.69 (CH_3). IR (cm^{-1}): 3380, 2930, 2858, 1749, 1604, 1510, 1385, 1363, 1220, 1172, 1149, 1088, 1032, 1016, 872, 835, 757. MALDI-MS: $[MNa]^+$ 786.2563 (calcd. 786.2556). Anal. Calcd for $C_{37}H_{47}F_2NO_{10}SiS$: C, 58.17; H, 6.20; N, 1.83. Found: C, 58.02; H, 6.26; N, 1.85.

The debenzylated azetidinone (31.5 mg, 0.041 mmol) was then dissolved in anhydrous THF (2.5 mL, teflon bottle), anhydrous pyridine (0.5 mL) followed by HF-pyridine complex (0.5 mL) were added and the solution was stirred for 24 h, diluted with ether (20 mL) and washed with sat. aq. $NaHCO_3$ (3 x 5 mL). The organic layer

was evaporated on celite and purified by dry column vacuum chromatography (4.3 x 2.0 cm) on silica gel eluting with a gradient of 0-20% MeOH in CH_2Cl_2 (v/v) to give the desired azetidinone **x** (9.8 mg, 37%) as a white solid.

^{1}H-NMR (300 MHz, acetone-d_6) δ: 7.55 (2H, d, J = 8.7 Hz), 7.47 (2H, d, J = 8.7 Hz), 7.36 (2H, dd, J = 5.6, 8.7 Hz), 7.29 (2H, dd, J = 4.8, 9.2 Hz), 7.06 (2H, d, J = 8.7 Hz), 7.03 (2H, d, J = 9.0 Hz), 4.98 (1H, d, J = 2.5 Hz), 4.68 (1H, bs), 4.58 (1H, bs), 4.38 (1H, bs), 4.27 (1H, bs), 3.89-3.80 (3H, m), 3.66 (1H, d, J = 10.6 Hz), 3.54-3.36 (5H, m), 3.24-3.14 (2H, m), 2.00-1.86 (4H, m). ^{13}C-NMR (75 MHz, acetone-d_6) δ: 168.48, 151.29, 143.63, 139.23, 136.09 (C), 129.37, 129.29, 129.19, 124.97, 120.05, 119.94, 117.49, 117.18, 116.46, 116.18 (CH), 82.17, 80.18, 76.78, 74.49, 73.79, 72.42 (CH), 63.67 (CH_2), 62.35, 61.63 (CH), 54.06, 38.62, 26.75 (CH_2). IR (cm^{-1}): 3364, 2924, 1734, 1509, 1388, 1220, 1148, 1102, 872, 835, 769. MALDI-MS ($C_{31}H_{33}F_2NO_{10}S$): $[MNa]^+$ 672.1744 (calcd. 672.1691).

Example 7



xi

$LiAlH_4$ (57 mg, 1.5 mmol) and $AlCl_3$ (200 mg, 1.5 mmol) were suspended in anhydrous ether (15 mL), refluxed for 30 min and cooled to 0°C. The azetidinone **x** obtained in Example 6 (41.3 mg, 0.054 mmol) dissolved in anhydrous ether (5 mL) was added and

after stirring at 0°C for 10 min, sat. aq. $NaHCO_3$ (1 mL) was added dropwise. The suspension was evaporated on celite and purified by dry column vacuum chromatography (4.2 x 2.0 cm) on silica gel eluting with a gradient of 0-20% MeOH in CH_2Cl_2 (v/v) to give the corresponding azetidine (38.2 mg, 94%) as a white foam.

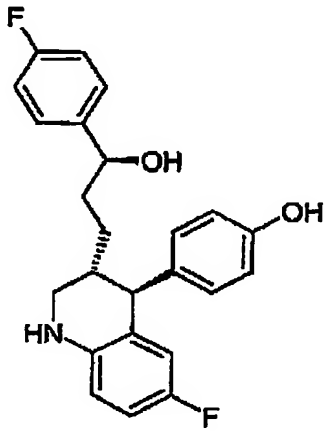
^{1}H-NMR (300 MHz, acetone-d_6) δ: 7.58 (2H, d, J = 8.7 Hz), 7.47 (2H, d, J = 8.7 Hz), 7.29 (2H, dd, J = 5.6, 8.7 Hz), 7.05 (2H, t, J = 8.7 Hz), 6.88 (2H, t, J = 9.0 Hz), 6.37 (2H, dd, J 4.7, 9.0 Hz), 4.71 (1H, t, J = 5.5 Hz), 4.61 (1H, d, J = 5.0 Hz), 4.49 (2H, d, J = 6.8 Hz), 4.30 (1H, bs), 4.17 (1H, t, J = 7.2 Hz), 3.92-3.83 (3H, m), 3.74-3.66 (1H, m), 3.57-3.40 (5H, m), 3.32-3.15 (2H, m), 2.63-2.56 (1H, m), 1.82-1.56 (4H, m), 0.87 (9H, s), 0.04 (3H, s), -0.17 (3H, s). ^{13}C-NMR (75 MHz, acetone-d_6) δ: 164.97, 161.76, 159.31, 156.21, 150.76, 150.47, 150.45, 143.77, 143.11, 143.07 (C), 129.35, 129.22, 124.60, 116.95, 116.65, 116.48, 116.19, 114.86, 114.75 (CH), 82.15, 80.21, 76.81, 75.43, 74.99, 74.52, 72.41 (CH), 63.70, 57.54, 53.95 (CH_2), 43.62 (CH), 39.47, 31.22 (CH_2), 27.20 (CH_3), 19.70 (C), -3.40, -3.68 (CH_3). IR (cm^{-1}): 3377, 2930, 2856, 1605, 1508, 1472, 1361, 1252, 1222, 1147, 1090, 1015, 871, 836, 776, 760. MALDI-MS ($C_{37}H_{49}F_2NO_9SSi$): $[MNa]^+$ 772.2767 (calcd. 772.2763).

The azetidine obtained above (34.3 mg, 0.046 mmol) was dissolved in anhydrous THF (2.5 mL, teflon bottle), anhydrous pyridine (0.5 mL) followed by HF·pyridine complex (0.5 mL) were added and the solution was stirred for 14 h, diluted with ether (20 mL) and washed with sat. aq. $NaHCO_3$ (3 x 5 mL). The organic layer was evaporated on celite and purified by dry column vacuum chromatography (4.9 x 2.0 cm) on silica gel eluting with a gradient of 0-18% MeOH in CH_2Cl_2 (v/v) to give the desired azetidine **XI** (20.2 mg, 69%) as a colourless oil.

^{1}H-NMR (300 MHz, acetone-d_6) δ: 7.61 (2H, d, J = 8.1 Hz), 7.48

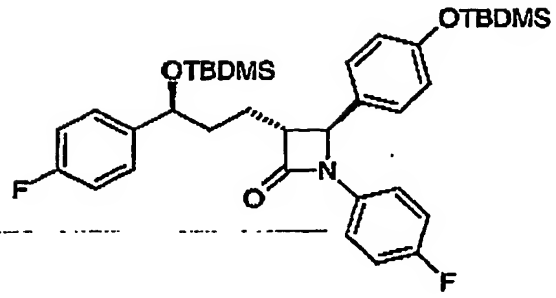
(2H, d, J = 8.7 Hz), 7.30 (2H, dd, J = 5.6, 8.7 Hz), 7.04 (2H, t, J = 8.7 Hz), 6.89 (2H, m), 6.38 (2H, dd, J = 4.4, 8.7 Hz), 4.60 (2H, d, J = 4.4 Hz), 4.52 (1H, d, J = 6.8 Hz), 4.45 (1H, d, J = 2.5 Hz), 4.29 (2H, d, J = 4.4 Hz), 4.19 (1H, t, J = 6.8 Hz), 4.03-3.83 (3H, m), 3.80-3.67 (1H, m), 3.60-3.31 (6H, m), 3.25 (1H, p, J = 4.4 Hz), 2.62 (1H, dd, J = 7.5, 14.3 Hz), 1.92-1.82 (1H, m), 1.78-1.61 (3H, m). ^{13}C-NMR (75 MHz, acetone-d_6) δ: 164.04, 155.14, 149.92, 149.71, 149.47, 142.77, 129.48 (C), 128.19, 128.16, 128.05, 123.52, 123.03, 115.87, 115.58, 115.39, 115.32, 115.05, 113.78, 113.69, 113.61, 113.51 (CH), 81.09, 79.15, 75.76, 73.98, 73.46, 72.75, 71.36 (CH), 62.63, 56.60, 52.88 (CH_2), 42.68 (CH), 37.52, 29.61 (CH_2). IR (cm^{-1}): 3370, 2933, 1605, 1508, 1474, 1360, 1220, 1146, 1087, 1015, 873, 823, 771. MALDI-MS ($C_{31}H_{35}F_2NO_9S$): $[MH-H_2O]^+$ 618.1973 (calcd. 618.1973); $[M]^+$ 635.1996 (calcd. 635.2001); $[MNa]^+$ 658.1900 (calcd. 658.1898).

Example 8



XII

a)



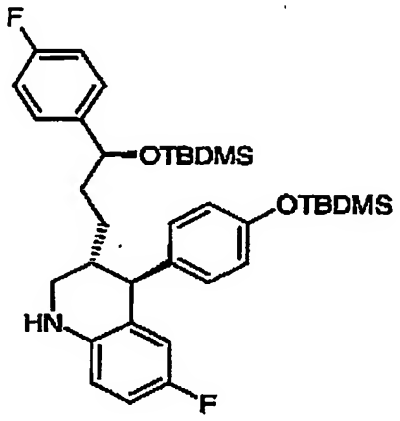
XIIa

Ezetimibe (commercially obtained or synthesized according to Wu, G. Z. et al., *J. Org. Chem.* **1999**; 279 mg, 0.681 mmol) was dissolved in anhydrous DMF (5 mL), imidazole (262 mg, 3.84 mmol) and TBDMSCl (500 mg, 3.32 mmol) were added sequentially and the solution was stirred for 5 h followed by addition of 50% sat. aq. $NaHCO_3$ (50 mL). After extraction with EtOAc (4 x 20 mL), the combined organic layer was washed successively with sat. aq. $NaHCO_3$ (20 mL) and H_2O (20 mL), evaporated on celite and purified by dry column vacuum chromatography (3.8 x 3.3 cm) on silica gel eluting with a gradient of 0-10% EtOAc in hexane (v/v) to give the fully silylated azetidinone **XIIa** (424 mg, 97%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.25-7.21 (4H, m), 7.17 (2H, d, J = 8.1 Hz), 6.98 (2H, t, J = 8.7 Hz), 6.91 (2H, t, J = 8.7 Hz), 6.83 (2H, d, J = 8.1 Hz), 4.66 (1H, t, J = 5.6 Hz), 4.51 (1H, d, J = 2.5 Hz), 3.08-3.02 (1H, m), 1.96-1.78 (4H, m), 0.98 (9H, s), 0.88 (9H, s), 0.20 (6H, s), 0.02 (3H, s), -0.16 (3H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.27, 163.28, 160.27, 160.04, 157.06, 155.71, 140.58, 140.54, 133.89, 133.86 (C), 129.99, 127.22, 127.11, 126.94, 120.56, 118.24, 118.15, 115.74, 115.44, 114.99, 114.72 (CH), 73.84, 61.08, 60.44 (CH_2), 38.08 (CH_2), 25.90, 25.68 (CH_3), 24.75 (CH_2), 18.26, 18.24 (C), -4.28, -4.52, -4.83 (CH_3).

IR (cm^{-1}): 2954, 2930, 2858, 1752, 1607, 1510, 1385, 1259, 1223, 1101, 1085, 914, 834, 778. MALDI-MS: $[MH-TBDMSOH]^+$ 506.2329 (calcd. 506.2327); $[MH]^+$ 638.3289 (calcd. 638.3297); $[MNa]^+$ 660.3117 (calcd. 660.3117). Anal. Calcd for $C_{36}H_{49}F_2NO_3Si_2$: C, 67.78; H, 7.74; N, 2.20. Found: C, 67.70; H, 7.60; N, 2.02.

b)



XIIb

$LiAlH_4$ (57 mg, 1.5 mmol) and $AlCl_3$ (200 mg, 1.5 mmol) were suspended in anhydrous ether (15 mL), refluxed for 40 min and cooled to 0°C. The fully silylated azetidinone **XIIa** obtained under step 8a) (180.8 mg, 0.283 mmol) dissolved in anhydrous ether (5 mL) was added and after stirring at 0°C for 30 min, H_2O (1 mL) was added dropwise. The suspension was evaporated on celite and purified by dry column vacuum chromatography (3.5 x 3.3 cm) on silica gel eluting with a gradient of 0-50% CH_2Cl_2 in hexane (v/v) to give the desired bicyclic amine **XIIb** (110.8 mg, 63%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.18-7.14 (2H, m), 6.95 (2H, t, J = 8.7 Hz), 6.88 (2H, d, J = 8.7 Hz), 6.74 (2H, d, J = 8.1 Hz), 6.68 (1H, dd, J = 2.8, 8.4 Hz), 6.44 (1H, dd, J = 6.5, 8.7 Hz), 6.38 (1H, dd, J = 2.8, 9.6 Hz), 4.48 (1H, dd, J = 5.0, 6.8 Hz), 3.78 (1H, bs), 3.61 (1H, d, J = 7.5 Hz), 3.26 (1H, dd, J = 3.1,

11.2 Hz), 2.91 (1H, dd, J = 7.8, 11.5 Hz), 1.91-1.85 (1H, m), 1.68-1.44 (3H, m), 1.16-1.04 (1H, m), 0.99 (9H, s), 0.80 (9H, s), 0.20 (6H, s), 0.06 (3H, s), -0.21 (3H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 163.60, 160.36, 157.37, 154.27, 141.53, 141.01, 138.13 (C), 130.07, 127.56, 127.46, 125.58, 125.50, 120.01, 117.27, 116.98, 115.17, 114.89, 114.78, 114.08, 113.79 (CH), 74.64, 48.97 (CH), 44.52 (CH_2), 39.89 (CH), 38.67, 28.28 (CH_2), 26.00, 25.90 (CH_3), 18.38, 18.32 (C), -4.16, -4.43, -4.77 (CH_3). IR (cm^{-1}): 2955, 2930, 2858, 1607, 1506, 1472, 1408, 1361, 1258, 1222, 1170, 1144, 1085, 1006, 915, 837, 808, 779, 735, 667. MALDI-MS ($C_{36}H_{51}F_2NO_2Si_2$): $[MH-TBDMSOH]^+$ 492.2517 (calcd. 492.2534); $[M]^+$ 623.3414 (calcd. 623.3426). Anal. Calcd for $C_{36}H_{51}F_2NO_2Si_2$: C, 69.30; H, 8.24; N, 2.24. Found: C, 69.47; H, 8.32; N, 2.15.

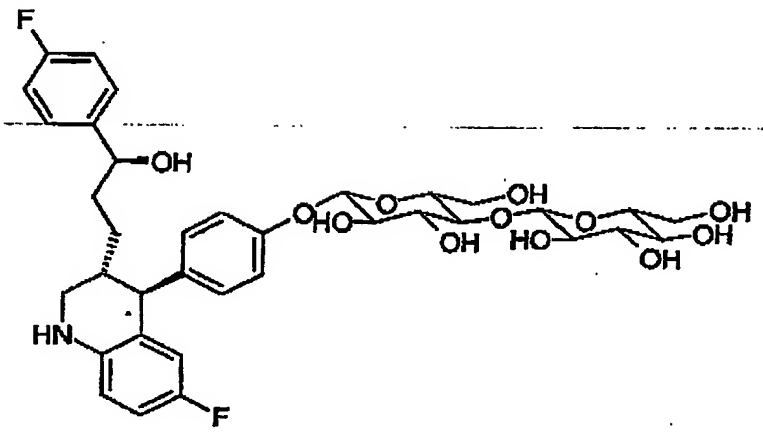
c)

The bicyclic amine **XIIb** obtained under step 8b) (39.8 mg, 0.064 mmol) was dissolved in THF (5 mL), TBAF (0.5 mL, 1M in THF) was added and the solution was stirred for 21 h, evaporated on celite and purified by dry column vacuum chromatography (3.7 x 2.0 cm) on silica gel eluting with a gradient of 0-100% EtOAc in hexane (v/v) to give the desired amine **XII** (27.7 mg, quant.) as a yellowish solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.19-7.15 (2H, m), 6.97 (2H, t, J = 8.7 Hz), 6.87 (2H, d, J = 8.4 Hz), 6.74-6.66 (3H, m), 6.46 (1H, dd, J = 5.0, 8.7 Hz), 6.38 (1H, dd, J = 2.2, 9.0 Hz), 5.54 (1H, bs), 4.52 (1H, t, J = 6.5 Hz), 3.61 (1H, d, J = 7.2 Hz), 3.26 (1H, dd, J = 3.4, 11.5 Hz), 2.90 (1H, dd, J = 7.5, 11.5 Hz), 1.95-1.86 (1H, m), 1.78-1.68 (2H, m), 1.52-1.41 (1H, m), 1.19-1.06 (1H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 163.55, 160.30, 157.10, 154.25, 154.00, 140.44, 139.95, 139.90, 137.07 (C), 129.90, 127.46, 127.36, 125.24, 116.99, 116.70, 115.28, 115.26, 115.21, 115.15, 115.00, 114.95, 114.84, 113.91, 113.61 (CH), 73.94, 48.53 (CH), 43.98 (CH_2), 39.73 (CH), 36.43, 27.95 (CH_2). IR (cm^{-1}): 3335, 2925, 2853, 1607, 1511, 1223, 913, 836, 744. MALDI-MS

($C_{24}H_{23}F_2NO_2$): $[MH-H_2O]^+$ 378.1661 (calcd.378.1670); $[M]^+$ 395.1689 (calcd. 395.1670)

Example 9



XIII

The bicyclic amine **XIIb** obtained in step 8b) (503 mg, 0.806 mmol) was dissolved in THF (15 mL) at 0°C, TBAF (1.5 mL, 1M in THF) was added and the solution was stirred at 0°C for 1.5 h, diluted with EtOAc (50 mL) and washed successively with sat. aq. $NaHCO_3$ (20 mL) and H_2O (20 mL). The organic layer was evaporated on celite and purified by dry column vacuum chromatography (3.4 x 3.3 cm) on silica gel eluting with a gradient of 0-30% EtOAc in hexane (v/v) to give the corresponding phenol (344.2 mg, 84%) as a light yellow foam.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.16 (2H, dd, J= 5.6, 8.1 Hz), 6.95 (2H, t, J = 8.7 Hz), 6.90 (2H, d, J = 8.7 Hz), 6.72 (2H, d, J = 8.7 Hz), 6.72-6.67 (1H, m), 6.48 (1H, dd, J = 4.4, 8.7 Hz), 6.39 (1H, dd, J = 2.7, 9.6 Hz), 4.49 (1H, dd, J = 5.6, 6.8 Hz), 4.40 (1H, bs), 3.61 (1H, d, J = 7.5 Hz), 3.28 (1H, dd, J = 2.7, 11.2 Hz), 2.92 (1H, dd, J = 8.1, 11.2 Hz), 1.93-1.87 (1H, m), 1.73-1.47 (3H, m), 1.20-1.15 (1H, m), 0.81 (9H, s), 0.06 (3H, s), -0.20 (3H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 163.16, 159.93, 157.15, 154.03, 141.13, 141.09, 140.43, 140.40, 137.05 (C), 129.95,

127.21, 127.11, 125.69, 125.62, 116.92, 116.62, 115.23, 114.98, 114.87, 114.83, 114.55, 113.83, 113.53 (CH), 74.36, 48.77 (CH), 44.49 (CH_2), 39.78 (CH), 38.46, 28.07 (CH_2), 25.81 (CH_3), 18.17 (C), -4.52, -4.90 (CH_3). IR (cm^{-1}): 3338, 2954, 2929, 2857, 1606, 1508, 1475, 1462, 1361, 1251, 1221, 1084, 836, 775, 760. MALDI-MS ($C_{30}H_{37}F_2NO_2Si$): $[MH-TBDMSOH]^+$ 378.1657 (calcd. 378.1670); $[M]^+$ 509.2553 (calcd. 509.2562).

The phenol obtained above (79 mg, 0.15 mmol) and 2,3,6-tri-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-β-D-glucopyranosyl)-α-D-glucopyranosyl 1-(2,2,2-trichloroacetimidate) (prepared according to Buijsman, R. C. et al., *Bioorg. Med. Chem.* **1999**, 7, 1881-1890; 267 mg, 0.34 mmol) were then dissolved in anhydrous CH_2Cl_2 (2 mL) at -25°C and $BF_3{\cdot}OEt_2$ in CH_2Cl_2 (1:9 (v/v), 0.10 mL, 0.08 mmol) was added. After stirring for 2.5 h at -25 to -20°C, additional $BF_3{\cdot}OEt_2$ (0.05 mL, 0.39 mmol) was added and after additional 1 h at -25 to -20°C, sat. aq. NH_4Cl (10 mL) and EtOAc (10 mL) were added. The layers were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic layer was washed successively with sat. aq. $NaHCO_3$ (10 mL) and H_2O (10 mL), evaporated on celite and purified by dry column vacuum chromatography (4.5 x 2.0 cm) on silica gel eluting with a gradient of 0-70% EtOAc in hexane (v/v) to give the glycosylated amine (169 mg, 97%) as a white foam.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.12 (2H, dd, *J*= 5.6, 8.7 Hz), 6.94-6.84 (6H, m), 6.66 (1H, dt, *J* = 2.5, 8.1 Hz), 6.42 (1H, dd, *J* = 4.4, 8.7 Hz), 6.29 (1H, dd, *J* = 2.7, 9.6 Hz), 5.29-4.90 (6H, m), 4.54-4.43 (3H, m), 4.37 (1H, dd, *J* = 4.4, 12.5 Hz), 4.16-4.02 (2H, m), 3.86 (1H, t, *J* = 9.0 Hz), 3.77-3.64 (2H, m), 3.60 (1H, d, *J* = 7.5 Hz), 3.23 (1H, dd, *J* = 2.7, 11.5 Hz), 2.88 (1H, dd, *J* = 8.1, 11.2 Hz), 2.07-1.96 (21H, m), 1.87-1.75 (1H, m), 1.70-1.38 (3H, m), 1.13-0.97 (1H, m), 0.76 (9H, s), -0.10 (3H, s), -0.25 (3H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 170.38, 170.09, 169.67,

169.47, 169.20, 168.96, 163.25, 160.01, 156.95, 155.27, 153.85, 141.10, 140.73, 140.10 (C), 129.91, 127.21, 127.11, 124.80, 116.68, 114.83, 114.56, 113.62 (CH), 100.71, 98.80, 76.33, 74.20, 72.81, 72.69, 72.42, 71.89, 71.48, 71.27, 67.63 (CH), 61.84, 61.42 (CH_2), 48.71 (CH), 44.19 (CH_2), 39.61 (CH), 38.27, 27.85 (CH_2), 25.64, 20.67, 20.58, 20.43 (CH_3), 17.96 (C), -4.76, -5.14 (CH_3). IR (cm^{-1}): 2955, 2858, 1756, 1506, 1368, 1223, 1049, 837, 770. MALDI-MS ($C_{56}H_{71}F_2NO_{19}Si$): $[MNa]^+$ 1150.4235 (calcd. 1150.4255).

The glycosylated amine obtained above (370 mg, 0.328 mmol) was then dissolved in THF (10 mL), TBAF (1.0 mL, 1M in THF) was added and the solution was stirred for 27 h, diluted with EtOAc (40 mL) and washed successively with sat. aq. $NaHCO_3$ (15 mL) and H_2O (15 mL). The organic layer was evaporated and the crude intermediate [MALDI-MS ($C_{50}H_{57}F_2NO_{19}$): $[MNa]^+$ 1036.3394 (calcd. 1036.3391)] was dissolved in MeOH/Et_3N/THF (12 mL, 1:1:2 (v/v/v)), H_2O (10.5 mL) was added dropwise and the solution was stirred for 18 h. sat. aq. $NaHCO_3$ (1 mL) was added dropwise and the suspension was evaporated on celite and purified by dry column vacuum chromatography (4.0 x 3.3 cm) on silica gel eluting with a gradient of 0-25% MeOH in EtOAc (v/v) to give the desired bicyclic amine **XIII** (80.5 mg, 34%) as a white solid after coevaporation with hexane (20 mL).

^{1}H-NMR (300 MHz, CD_3OD) δ: 7.20 (2H, dd, J= 5.6, 8.7 Hz), 7.02-6.93 (6H, m), 6.65 (1H, dt, J = 2.5, 8.7 Hz), 6.54 (1H, dd, J = 5.0, 8.7 Hz), 6.23 (1H, dd, J = 2.5, 10.0 Hz), 4.94 (1H, d, J = 7.5 Hz), 4.47-4.43 (2H, m), 3.92 (2H, bs), 3.90 (1H, d, J = 10.6 Hz), 3.72-3.52 (6H, m), 3.43-3.22 (5H, m), 2.86 (1H, dd, J = 8.1, 11.8 Hz), 1.96-1.84 (1H, m), 1.80-1.68 (2H, m), 1.50-1.35 (1H, m), 1.17-1.03 (1H, m). ^{13}C-NMR (75 MHz, CD_3OD) δ: 164.71, 161.49, 157.30, 155.12, 142.58, 141.98, 141.95, 140.78 (C), 130.89, 128.83, 128.72, 126.64, 126.56, 117.52, 117.36, 117.09, 115.86, 115.57 (CH), 104.44, 101.98, 80.21, 78.01, 77.76, 76.49,

76.22, 74.83, 74.58, 74.41, 71.29 (CH), 62.39, 61.63 (CH_2), 50.00 (CH), 45.09 (CH_2), 40.95 (CH), 37.38, 29.09 (CH_2). MALDI-MS ($C_{36}H_{43}F_2NO_{12}$): $[MNa]^+$ 742.2654 (calcd. 742.2651).

Example 10

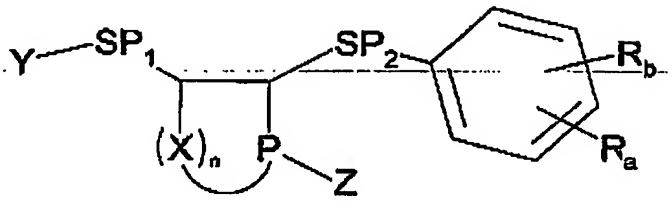
The compounds of the invention and ezetimibe (commercially obtained or prepared according to Wu, G. Z. et al., *J. Org. Chem.* **1999**) together with the glucuronide (the metabolite of ezetimibe, prepared according to Vaccaro, W. D.; Davis, H. R. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 313-318) as appropriate reference compounds were evaluated by well-established methods to determine their inhibition of cholesterol uptake in rabbit brush border membrane vesicles (BBMV) (Table 1). Briefly, the scavenger receptor-mediated uptake of radiolabelled cholesterol ester from the loaded donor particles into the BBMV bilayer was measured in the presence of various compounds of the invention and appropriate reference compounds (Hauser, H. et al., *Biochemistry* **1998**, *37*, 17843-17850; Werder, M. et al., *Biochemistry* **2001**, *40*, 11643-11650; Boffelli, D. et al., *FEBS Lett.* **1997**, *411*, 7-11.)

Table 1:

Compound	applied in donor SUV (9 mol%) Inhibition in (%)
Ezetimibe	16 ± 4
Glucuronide	19 ± 4
VI	30 ± 4
VII	22 ± 2
VIII	15 ± 3
IXb	20 ± 5
IX	27 ± 4
X	15 ± 3
XI	20 ± 5

Claims

1. A compound according to formula I



I

wherein

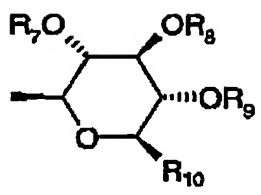
P represents -N< or -C=,

X represents independently of each other $-CH_2-$, CR_1 (sp_2-hybridised), O, -NH-, =N-, -CO- or -CS-, wherein R_1 represents H or NR_2, wherein R_2 represents H or lower alkyl, which optionally is linked to Z such that a bicyclic structure is formed;

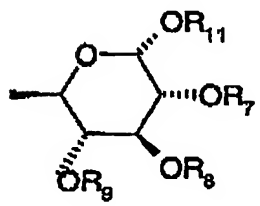
n represents 1 or 2,

R_a represents H, lower alkyl, $-OR_3$, $-O(CO)R_3$, $-O(CO)OR_3$, $-O(CO)NR_3R_4$, $-NR_3R_4$, $-NR_3(CO)R_4$, $-COOR_3$, $-CONR_3R_4$, $-CH=CHCOOR_3$, $-CF_3$, -CN, $-NO_2$, SO_3H, PO_3H or halogen, wherein R_3 and R_4 represent H or lower alkyl,

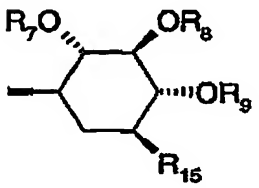
R_b represents H, OH, $-OSO_2Me$, $-OSO_2W$ wherein W represents optionally substituted aryl or heteroaryl, $-OCO(CHOH)_2COOR_5$ wherein R_5 represents H or lower alkyl; or represents the formula $-Sp_3-R_6$,
wherein Sp_3 represents a covalent bond, -O-, $-OCH_2-$, $-OSO_2CH_2-$, $-OSO_2-$, $-OSO_2-(p)C_6H_4O-$ and R_6 represents one of carbohydrate structures A-D:



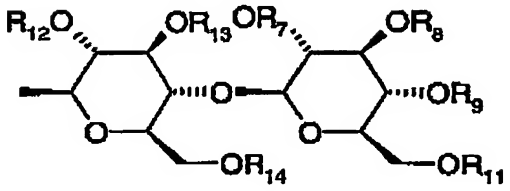
A



B



C



D

wherein

R_7, R_8, R_9, R_{11}, R_{12}, R_{13} and R_{14} represent independently of each other H, lower alkyl, aryl(lower alkyl), -CO-lower alkyl, -CO-aryl, $-SO_3^-$ or $-PO_3^-$,

R_{10} represents $-CH_2OR_{16}$ or $-COOR_{17}$, and

R_{15} represents $-CH_2OR_{16}$, $-COOR_{17}$, $-CH_2NH_2$, $-CH_2OPO_3^-$ or $-CH_2OSO_3^-$, wherein R_{16} and R_{17} independently of each other represent H, lower alkyl, aryl(lower alkyl), -CO-lower alkyl, -CO-aryl, $-SO_3^-$ or $-PO_3^-$,

Z represents optionally substituted aryl or heteroaryl,

Sp_1 represents a spacer unit, such as a straight-chain or branched lower alkyl group $-(CH_2)_p-$, wherein p is from 2-6, which is unsubstituted, mono or poly-substituted by -OH, $-OR_{18}$, halogen or cyano group, wherein one or more $-CH_2-$ groups may independently be replaced by -O-, -CO-, -CO-O-, -O-CO-, $-NR_{19}-$, $-NR_{19}-CO-$, $-CO-NR_{19}-$, -CH=CH-, -C≡C- -and wherein R_{18} and R_{19} represent a hydrogen atom or lower alkyl;

Sp_2 represents an optional spacer unit, such as a covalent bond or a straight-chain or branched lower alkyl group -

$(CH_2)_q$-, wherein q is from 1-6, which is unsubstituted, mono or poly-substituted by -OH, $-OR_{20}$, halogen or cyano group, wherein one or more $-CH_2-$ groups may independently be replaced by -O-, -CO-, -CO-O-, -O-CO-, $-NR_{21}-$, $-NR_{21}-$CO-, $-CO-NR_{21}-$, -CH=CH-, -C≡C- -and wherein R_{20} and R_{21} represents a hydrogen atom or lower alkyl;

Y represents optionally substituted aryl or heteroaryl,

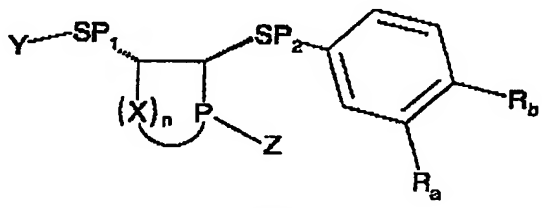
with the proviso, that if P = -N<, n=1, X = -CO- and Sp_3 represents a covalent bond, R' may not represent carbohydrate structures A or D for Sp_3 = -O- and R_6 may not represent carbohydrate B for Sp_3 = $-OCH_2-$.

2. A compound according to claim 1 wherein P = -N<, n = 1 and X = -CO-, -CS-, $-CH_2-$ or -NH-.

3. A compound according to claim 1 wherein P = -N< and $-(X)_n-$ = -OOC-, -COO-, -CONH-, -CH=N-.

4. A compound according to claim 1 wherein P = -C= and $-(X)_n-$ = -NH-N= or -O-N=.

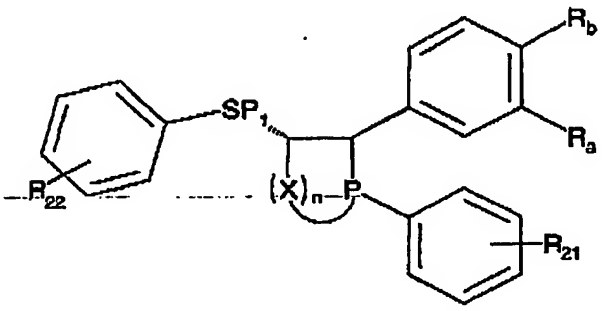
5. A compound according to claim 1 having the formula IVa



IVa

wherein R_a, R_b, Sp_1, Sp_2, P, X, Y, Z and n are as defined in claim 1.

6. A compound according to claim 1 having the formula IVb,



IVb

wherein R_a, R_b, Sp_1, P, X and n are as defined hereinabove and wherein R_{21} and R_{22} represent H, lower alkyl, lower alkoxy or halogen.

7. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any preceding claim with a pharmaceutically acceptable carrier.

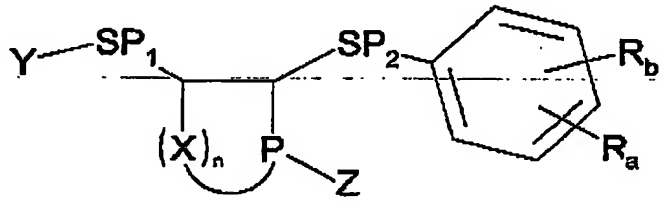
8. A pharmaceutical composition according to claim 6 for the treatment or prevention of artheriosclerosis or for the reduction of cholesterol levels.

9. A kit comprising a pharmaceutical composition according to claim 6 for use in the treatment or prevention of artheriosclerosis or for the reduction of cholesterol levels

10. A method for the treatment or prevention of artheriosclerosis or for the reduction of cholesterol levels comprising administering to a subject in need of such treatment an effective amount of a compound according to any preceding claim.

Abstract

The present invention relates to novel hypocholesterolemic compounds of formula I



I

useful in the treatment and prevention of atherosclerosis and for the reduction of cholesterol levels as well as to pharmaceutical compositions comprising said compounds alone or in combination with other active agents